Rhythm Pharmaceuticals Announces Oral MC4R Agonist Bivamelagon Achieved Statistically Significant, Clinically Meaningful BMI Reductions in Placebo-controlled Phase 2 Trial in Acquired Hypothalamic Obesity

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-- Bivamelagon achieved BMI reductions in patients with acquired hypothalamic obesity of -9.3% and -7.7% in 600mg and 400mg cohorts, respectively, at 14 weeks --

-- Post-hoc analysis showed BMI reductions in bivamelagon trial were consistent with BMI reductions achieved by setmelanotide in past trials in similar patient populations --

-- Patients in both 600mg and 400mg cohorts achieved mean reduction of -2.8 points in most hunger scores --

-- Limited instances of localized hyperpigmentation observed --

-- Rhythm to request End-of-Phase 2 meeting with U.S. FDA in order to pursue registrational path for bivamelagon in acquired hypothalamic obesity --

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

BOSTON, July 09, 2025 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients living with rare neuroendocrine diseases, today announced positive topline results from its Phase 2 trial evaluating bivamelagon (formerly LB54640), an investigational oral melanocortin-4 receptor (MC4R) agonist, in patients with acquired hypothalamic obesity. Bivamelagon achieved statistically significant and clinically meaningful reductions in body mass index (BMI) at 14 weeks of treatment, consistent with BMI reductions achieved with setmelanotide therapy in similar patient populations in past trials. Rhythm in-licensed bivamelagon from LG Chem, Ltd in January 2024.

In the 14-week, double-blind, four-arm, placebo-controlled portion of the trial, bivamelagon achieved:

- -9.3% BMI reduction from baseline in the 600mg cohort (n=8) (p-value=0.0004);
- -7.7% BMI reduction from baseline in the 400mg cohort (n=7) (p-value=0.0002);
- -2.7% BMI reduction from baseline in the 200mg cohort (n=6) (p-value=0.0180); and
- BMI for patients in the placebo cohort (n=7) increased by 2.2% over 14 weeks.

“We are excited by these results, which suggest bivamelagon has the potential to treat patients with acquired hypothalamic obesity, and has established an appropriate dose range for future clinical evaluation. Unlike in studies evaluating general obesity, once again we observed no placebo effect in this study,” said David Meeker, M.D., Chair, Chief Executive Officer and President of Rhythm Pharmaceuticals. “We look forward to engaging with U.S. and European regulatory authorities to seek alignment on a Phase 3 trial design as we continue advancing bivamelagon.”

In a post-hoc analysis comparing the randomized Phase 2 results to results from prior setmelanotide trials, bivamelagon demonstrated BMI reductions consistent with BMI reductions achieved with setmelanotide therapy as observed in similar patient populations at comparable dosing durations. In this post-hoc comparison of the subset of setmelanotide patients who demonstrated study compliance and were not on concomitant GLP1 therapy (no patients who enrolled in the Phase 2 bivamelagon trial were on concomitant GLP1 therapy), setmelanotide and bivamelagon achieved:

- -9.7% and -10.5% mean BMI reductions achieved in a pooled patient population (n=59; n=64) from Phase 2 and Phase 3 trials of setmelanotide therapy at 12 weeks and 16 weeks, respectively; as compared to:
- -8.8% and -10.1% mean BMI reductions achieved in patients (400mg n=6; 600mg n=7) at 14 weeks of bivamelagon therapy.

In addition, patients reported meaningful reductions in their ‘most’ hunger scores at 14 weeks on therapy compared to placebo, consistent with past setmelanotide trials and MC4R agonism. Patients in the 600mg (n=8) and 400mg (n=6) cohorts achieved a mean reduction greater than 2.8 points in their ‘most’ hunger scores measured on a 10-point scale at 14 weeks of bivamelagon therapy. Six patients in the 200mg arm achieved a mean reduction of 2.1 points in their ‘most’ hunger score, while patients on placebo therapy reported a mean increase of 0.8 points in their mean ‘worst’ hunger score.

Bivamelagon demonstrated safety and tolerability results consistent with MC4R agonism and mechanism of action during the placebo-controlled portion of the trial. During the placebo-controlled portion of the trial, one patient discontinued therapy due to a serious adverse event (rectal bleeding). The most common reported adverse events were episodes of diarrhea and nausea, the vast majority of which were mild or grade 1. There were reports of mild, localized hyperpigmentation from four patients, including one patient on placebo. A total of 27 patients completed the 14-week, placebo-controlled portion of the trial, and 26 of them transitioned into the open-label extension of the trial and remained in that portion of the trial, as of July 7, 2025.

Next Steps
With these results in hand, Rhythm plans to seek input from U.S. and EU regulatory authorities on a Phase 3 trial design to advance bivamelagon in acquired hypothalamic obesity. The Company plans to request an End-of-Phase 2 meeting with the U.S. Food and Drug Administration (FDA) and to seek scientific advice from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). Rhythm also is refining the formulation of bivamelagon potentially to improve tolerability ahead of initiating a Phase 3 trial.

As previously announced, Rhythm will present results from this trial in a poster accepted as a late-breaking abstract and data from Rhythm's pivotal Phase 3 TRANSCEND trial evaluating setmelanotide in both a live oral presentation and a poster at The Endocrine Society's Annual Meeting (ENDO 2025) on July 12, 2025 in San Francisco.

About the Bivamelagon Phase 2 Trial
The Phase 2 trial is a randomized, placebo-controlled, double-blind study to assess efficacy and safety of bivamelagon (formerly LB54640) on safety, weight reduction, hunger, and quality of life in patients 12 years of age and older (n=28) with acquired hypothalamic obesity. In the randomized portion of the trial, patients took an oral daily dose of either bivamelagon, low (200 mg), middle (400 mg), or high (600 mg), or placebo for 14 weeks. Patients may continue on therapy in the open-label portion for up to 52 weeks.

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. Participants may register for the conference call here. A webcast of the call will also 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 at least 30 days following the call.

About Acquired Hypothalamic Obesity
Acquired hypothalamic obesity is a rare form of obesity that occurs following damage to the hypothalamic region of the brain, which includes the melanocortin-4 receptor (MC4R) pathway and is responsible for controlling physiological functions such as hunger and weight regulation. Acquired hypothalamic obesity most frequently follows the growth or surgical removal of craniopharyngioma, astrocytoma or other rare brain tumors. Additional causes of injury may include traumatic brain injury, stroke, or inflammation due to infection. Patients experience accelerated weight gain, a reduction in energy expenditure, and hyperphagia (a chronic pathological condition characterized by insatiable hunger, impaired satiety, and persistent abnormal food-seeking behaviors) leading to severe obesity within six to 12 months following tumor resection or other injury.

Rhythm estimates there are 5,000 to 10,000 people living with hypothalamic obesity in the U.S., 5,000 to 8,000 people living with hypothalamic obesity in Japan, and 3,500 to 10,000 people living with hypothalamic obesity in the E.U.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with rare neuroendocrine diseases. Rhythm's lead asset, IMCIVREE® (setmelanotide), an MC4R agonist designed to treat hyperphagia and severe obesity, is approved by the U.S. Food and Drug Administration (FDA) to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or genetically confirmed pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency. 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 2 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare diseases, as well as investigational MC4R agonists bivamelagon and RM-718, and 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 to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or 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).

In the European Union and the United Kingdom, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 2 years of age and above. In the European Union and the United Kingdom, setmelanotide should

be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use

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 BBS or POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity

Contraindication

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

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, suicidal ideation and depressed mood 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.

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmented 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

Most common adverse reactions (incidence ≥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 +1 (833) 789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. See section 4.8 of the Summary of Product Characteristics for information on reporting suspected adverse reactions in Europe.

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 our Phase 2 study to assess the efficacy and safety of bivamelagon in patients with acquired hypothalamic obesity and the potential for bivamelagon to treat hypothalamic obesity; the safety, efficacy, potential benefits of, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of bivamelagon, setmelanotide and other product candidates; the clinical design or progress of any of our products or product candidates at any dosage or in any indication; the potential benefits of any of the Company’s products or product candidates for any specific disease indication or at any dosage, including the potential benefits of bivamelagon and setmelanotide for patients with acquired hypothalamic obesity or congenital hypothalamic obesity; our participation in upcoming events and presentations, and the date, time and content thereof and the timing of any of the foregoing. 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, 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 associated with data analysis and reporting, our ability to successfully commercialize setmelanotide, our liquidity and expenses, our ability to retain our key employees and consultants, and to attract, retain and motivate qualified personnel, and general economic conditions, and the other important factors, including those discussed under the caption “Risk Factors” in Rhythm’s Quarterly Report on Form 10-Q for the three months ended March 31, 2025 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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