



Rhythm Pharmaceuticals Announces Topline Results from Phase 3 EMANATE Trial

March 16, 2026

-- Four substudies did not meet pre-specified primary endpoints --

-- Post hoc analyses show setmelanotide achieved statistically significant BMI reductions in patients with obesity due to a heterozygous variant of the POMC/PCSK1 and SRC1 (NCOA1) genes at 52 weeks --

-- Conference call planned for 4:30 p.m. ET today --

BOSTON, March 16, 2026 (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 the topline results from its EMANATE trial. The four substudies of this global, Phase 3 trial evaluating setmelanotide did not meet primary endpoints.

"We are grateful to the patients with rare, genetically-driven MC4R pathway diseases and investigators who participated in this trial," said David Meeker, MD, Chair, President and Chief Executive Officer of Rhythm Pharmaceuticals. "While we are disappointed the EMANATE substudies did not meet their primary endpoint, we are encouraged by compelling signals from additional analyses of the heterozygous POMC/PCSK1 and SRC1 substudies and learnings that sharpen our ability to identify true loss-of-function variants and inform the development of our next-generation MC4R agonists in rare genetically driven obesity indications."

Dr. Meeker continued, "These patients continue to face a profound unmet medical need, with no approved treatment options that target the underlying biology of their disease. These results provide important insights that support our commitment to advancing targeted therapies for patients with rare genetic obesities."

EMANATE was a global, randomized, double-blind, placebo-controlled Phase 3 trial designed to evaluate the efficacy and safety of setmelanotide in patients with rare, genetically-driven obesities of the MC4R pathway. The study comprised four independent genetic substudies in patients with obesity due to a heterozygous (Hets) variant of the POMC/PCSK1 gene, the LEPR gene, the SRC1 (NCOA1) gene, and the SH2B1 gene with patients randomized 1:1 to receive setmelanotide or placebo for 52 weeks.

EMANATE Topline Results

The primary endpoint was the difference in mean percent change in BMI from baseline to Week 52 versus placebo, analyzed in the modified intent-to-treat (ITT) population using prespecified multiple imputation to account for missing values and discontinuations. Topline results include:

- **POMC / PCSK1 Hets (N=78):** -4.3% placebo-adjusted reduction in BMI (p=0.15);
- **LEPR Hets (N=23):** -3.6% placebo-adjusted reduction in BMI (p=0.94);
- **SRC1 (NCOA1) (N=73):** -4.0% placebo-adjusted reduction in BMI (p=0.12); and
- **SH2B1 (N=121):** -1.7% placebo-adjusted reduction in BMI (p=0.43).

According to post hoc analyses based on last observation carried forward (LOCF) for missing values, setmelanotide achieved statistically significant and clinically meaningful BMI reductions at Week 52 in the modified intent-to-treat patient populations in the POMC/PCSK1 Hets and SRC1 substudies:

- -5.5% least-squares mean difference in BMI in POMC/PCSK1 Hets patients (n=78; p=0.0010); and
- -6.2% least-squares mean difference in BMI in SRC1 (NCOA1) patients (n=73; p<0.0001).

According to post hoc analyses of genetically confirmed patients who reached Week 52 of treatment, setmelanotide achieved statistically significant and clinically meaningful BMI reductions in patients who completed the 52-week trial in the POMC/PCSK1 Hets and SRC1 substudies:

- -9.7% placebo-adjusted reduction in BMI in POMC/PCSK1 Hets patients (n=41; p=0.0002); and
- -8.0% placebo-adjusted reduction in BMI in SRC1 (NCOA1) patients (n=29; p=0.0158).

No new safety signals were observed with setmelanotide in the EMANATE trial, and the safety profile was consistent with prior clinical studies and commercial experience. The most common treatment-emergent adverse events included skin hyperpigmentation, injection site reactions, nausea, vomiting, and headache.

Rhythm plans to continue the analysis of the EMANATE dataset and evaluate potential clinical development paths forward with SRC1 (NCOA1) and POMC with its next-generation MC4R agonists bivamelagon and RM-718. In addition, the Company will continue to evaluate the potential for MC4R agonism in the genes and gene families previously identified through the exploratory Phase 2 DAYBREAK trial, including the SEMA3 family, PHIP, TBX3 or PLXNA family.

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 4:30 p.m. ET today to discuss this update. Participants may register for the conference call [here](#). It is recommended that participants join the call ten minutes prior to the scheduled start.

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 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 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 $\geq 20\%$) 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 +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 the potential safety, efficacy, potential benefits of, and clinical design or progress of any of our products or product candidates at any dosage or in any indication; clinical design, enrollment, or progress, and preliminary, interim and final data readouts; potential benefits from our EMANATE topline results, including our ability to identify true loss-of-function variants and develop our next-generation MC4R agonists; potential regulatory submissions, approvals and timing thereof of setmelanotide, bivamelagon, or RM-718; 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 setmelanotide, bivamelagon or RM-718 for patients with MC4R pathway diseases; expectations surrounding pending and potential regulatory submissions and approvals, including within the United States, the EU and other regions; business strategy and plans, including regarding commercialization of setmelanotide in the United States, the EU and other regions; our participation in upcoming events and presentations; 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 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 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 discussed under the caption “Risk Factors” in Rhythm’s Annual Report on Form 10-K for the year ended December 31, 2025 and 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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