



Rhythm Pharmaceuticals Announces Promising Clinical Data in MC4R Pathway Heterozygous Obesity and Strategy for Further Development

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-- Stratifying Enrollment of MC4R Pathway Heterozygous (HET) Patients in Phase 2 Basket Study Based on Loss-of-Function (LOF) Variants --

-- Preliminary Data Show Consistent Weight Loss and Decreases in Hunger Observed in Patients with High-Impact LOF Variants

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-- Management to Host Conference Call at 8:30 am ET Today --

BOSTON, March 28, 2019 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq:RYTM), a biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders of obesity, today announced updated interim data from its ongoing Phase 2 basket study of setmelanotide in melanocortin-4 receptor (MC4R) pathway heterozygous (HET) obesity. In addition, the company unveiled plans to continue evaluating setmelanotide in HET obesity, with patients enrolled into cohorts based on their loss-of-function (LOF) variants.¹ This decision is based primarily on clinical results, which show a more consistent treatment benefit in patients with higher-impact LOF variants.

"We are committed to advancing setmelanotide as swiftly as possible, with the goal of addressing the severe, early-onset obesity and relentless hunger experienced by people living with rare genetic disorders of obesity," said Keith Gottesdiener, M.D., Chief Executive Officer of Rhythm. "Today's announcement marks an important milestone in our efforts to assess the full range of setmelanotide's potential applications. As part of our work to better understand the biological underpinnings of rare genetic disorders of obesity, we have identified a wide spectrum of heterozygous LOF variants and believe there is a relationship between LOF variant and impact on pathway function. This belief is corroborated by the new clinical data announced today, as patients with high-impact LOF variants experienced a more consistent and greater response to setmelanotide. The data also provide a compelling strategy for further development. We look forward to pursuing proof-of-concept in HET patients with high-impact LOF variants, while exploring setmelanotide's potential benefit in patients with other variant subgroups and leveraging our genotyping engine to accelerate HET patient identification broadly."

HET obesity is caused by the mutation of one of two genetic copies of a gene in the MC4R pathway and can include patients with heterozygous mutations in genes such as *POMC*, *PCSK1* and *LEPR*. While there are numerous individual case histories of HET patients with severe, early-onset obesity and hyperphagia, HET patients have variable penetrance of obesity. Variable penetrance of disease in patients with heterozygous variants is a phenomenon observed in many genetic disease states. In patients with HET obesity, Rhythm believes this variability may be driven by the type of LOF variant, with higher-impact LOF variants more substantially impairing MC4R pathway function and, therefore, increasing the likelihood of developing hyperphagia and, subsequently, severe obesity.

Rhythm's clinical development efforts are initially focused on achieving proof-of-concept in patients with well-characterized, high-impact LOF variants. Patients with these variants can present clinically with the same severe, early-onset obesity and hyperphagia characteristic of other rare genetic disorders of obesity. Rhythm estimates a prevalence of upwards of 20,000 severely obese people living with high-impact LOF variants in the United States. Rhythm will also explore setmelanotide's potential in cohorts of HET patients with other genetic variants, in order to drive understanding of HET biology and identify additional people who may be setmelanotide-responsive.

New Clinical Data from Phase 2 Basket Study in HET Obesity

Today, Rhythm announced preliminary data from 13 HET patients who were treated with setmelanotide, including four patients with high-impact LOF variants and nine patients with other LOF variants:

- All four patients with high-impact LOF variants remain on therapy, including two patients who have been on treatment for more than 29 weeks.² The first patient, who entered the study weighing 451 pounds, lost 40.5 pounds (nine percent body weight) and experienced a hunger score decrease of 90 percent after 37 weeks of treatment with setmelanotide. The second patient, who entered the study weighing 284 pounds, lost 49 pounds (17.3 percent body weight) and experienced a hunger score decrease of 71.4 percent after 29 weeks of treatment. The two additional patients have been on treatment for a short duration and are showing promising weight loss and hunger score decreases during dose titration.
- Five of nine patients with other LOF variants remain on therapy, with treatment durations ranging from seven to 74 weeks.

This includes the two responding patients on whom Rhythm reported data in June 2018. Across these five patients, one experienced a clinically-meaningful weight loss of greater than 10 percent, three experienced weight loss between five and eight percent, and one has been on treatment for a short duration and it is too early to assess response to therapy. Among the four response-evaluable patients, hunger score decreases ranged from 20 to 80 percent.

- Four of nine patients with other LOF variants discontinued treatment, including one patient who was discontinued due to lack of efficacy (previously reported in June 2018). The other three patients were discontinued following less than four weeks on therapy and therefore efficacy could not be evaluated. This includes the two patients on whom Rhythm reported in June 2018, both discontinued due to adverse events (AEs). In addition, one patient was withdrawn by the site for patient non-compliance.

Consistent with prior clinical experience, setmelanotide continues to be well-tolerated. There were no serious AEs reported and no new discontinuations due to AEs since those reported in June 2018.

Clinical Development Plans in HET Obesity

Rhythm plans to continue enrolling HET patients in its Phase 2 basket study in cohorts stratified by LOF variant. In addition to pursuing proof-of-concept in high-impact LOF variants, Rhythm also plans to explore setmelanotide's potential in additional patient cohorts, including patients with partial LOF or newly-characterized variants, patients with more common variants, and patients with composite HET variants. Rhythm expects patient enrollment to continue at least through the remainder of 2019, with updated data to follow in 2020. Rhythm anticipates that these data will help inform the most appropriate strategy to support the potential registration and approval of setmelanotide for the treatment of setmelanotide-responsive subgroups of HET obesity.

In parallel, Rhythm intends to further ongoing efforts to better understand HET obesity and facilitate patient identification. In order to add to the pool of high-impact variants, Rhythm is undertaking a comprehensive effort to screen and classify new and uncharacterized variants in the MC4R pathway, using both computational models for assessing variants and biochemical analysis of variants in *POMC*, *PCSK1*, and *LEPR* to assess functional impact. Rhythm estimates that there are thousands of potential new and uncharacterized HET variants in MC4R pathway genes. Additionally, the company plans to leverage the Rhythm Engine, a portfolio of programs including the GO-ID genotyping study, the TEMPO Registry and the Phase 2 basket study, to identify patients who may be eligible for treatment with setmelanotide, rapidly enroll eligible patients in the ongoing trial, and better characterize the ongoing impact and burden of disease on patients and their caregivers.

Upcoming Milestones Across Broader Setmelanotide Development Program

Rhythm is advancing its development program for setmelanotide toward key 2019 and 2020 milestones. The company expects to:

- Announce topline data from its ongoing pivotal Phase 3 trials in patients with pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity in the third quarter of 2019 and, if positive, submit concurrent New Drug Application filings to the U.S. Food and Drug Administration in the fourth quarter of 2019 or early 2020.
- Complete enrollment in its combined pivotal Phase 3 trial in Bardet-Biedl syndrome (BBS) and Alström syndrome in the second half of 2019, and to report topline data in 2020.
- Expand its ongoing Phase 2 basket study into additional MC4R pathway disorders in 2019, while continuing to enroll patients with POMC epigenetic disorders.

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 8:30 a.m. ET today to discuss these clinical data and review its strategy for further development in HET obesity. The conference call may be accessed by dialing (844) 498-0570 (domestic) and (409) 983-9726 (international) and referring to conference ID 7579267. A webcast of the conference call will be available in the Investors section of the Rhythm website at 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 90 days following the call.

About Setmelanotide

Setmelanotide is a potent, first-in-class, MC4R agonist in development for the treatment of rare genetic disorders of obesity. Setmelanotide activates MC4R, part of the key biological pathway that independently regulates energy expenditure and appetite. Variants in genes within the MC4R pathway are associated with unrelenting hunger and severe, early-onset obesity. Rhythm is currently developing setmelanotide as a replacement therapy for patients with monogenic defects upstream of MC4R, for whom there are no effective or approved therapies. The FDA has granted Breakthrough Therapy designation to setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome. The European Medicines Agency has also granted PRiority MEDicines (PRIME) designation for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R pathway.

About Rhythm Pharmaceuticals

Rhythm is a biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic disorders of obesity. Rhythm is currently evaluating the efficacy and safety of setmelanotide, the company's first-in-class MC4R agonist, in Phase 3 studies in patients with POMC deficiency obesity, LEPR deficiency obesity, BBS, and Alström

syndrome. Rhythm is dedicated to improving the understanding of severe obesity that results from specific genetic disorders. 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.

Forward-Looking Statements

This press release contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including statements regarding Rhythm's expectations regarding its estimates of patient population, its efforts to identify patients, anticipated timing for enrollment and design of clinical trials, anticipated timing for submission of New Drug Application filings, and timing of the release of results of clinical trials. Statements using word such as "expect", "anticipate", "believe", "may", "will", "plans" 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 outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, and expenses, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other reports we file 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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¹ A genetic variant is a difference in DNA sequences between an individual and the population.

² Total treatment duration as reported always includes any titration period, which can last 6-12 weeks before reaching a therapeutic dose.



Source: Rhythm Pharmaceuticals, Inc.