Rhythm Pharmaceuticals Announces Positive Topline Results from Pivotal Phase 3 Clinical Trials Evaluating Setmelanotide in POMC and LEPR Deficiency Obesities

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-- Both studies met primary and all key secondary endpoints with statistically significant and clinically meaningful results in reductions of weight and hunger --

-- Rhythm on track to complete rolling NDA submission to the FDA for both POMC and LEPR deficiency obesities in 4Q19 or 1Q20 --

-- Data from placebo withdrawal period provide evidence of drug action, validate clinical effect --

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

BOSTON, Aug. 07, 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 positive topline results from two pivotal, Phase 3 clinical trials evaluating setmelanotide, the company's melanocortin-4 receptor (MC4R) agonist, for the treatment of pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiency obesities. Both studies met their primary endpoints and all key secondary endpoints, demonstrating a statistically significant and clinically meaningful effect on weight loss and reductions in insatiable hunger, or hyperphagia, in patients with POMC and LEPR deficiency obesities.

"We believe these statistically significant data demonstrate setmelanotide's ability to induce marked weight loss and substantially reduce hunger and we are excited about the potential difference we can make in the lives of people with rare genetic disorders of obesity," said Keith Gottesdiener, M.D., Chief Executive Officer of Rhythm. "We believe these pivotal data are the first step towards making a positive impact for people affected by rare genetic disorders of obesity who have grown up with insatiable hunger and early-onset, rapid weight gain that often leads to debilitating comorbidities. We believe this milestone moves us closer to delivering a treatment for numerous MC4R pathway-driven disorders of obesity. We are working to advance setmelanotide to its first regulatory submission in POMC and LEPR deficiency obesities."

Eight of 10 patients with POMC deficiency obesity achieved the primary endpoint of greater than 10 percent weight loss over approximately one year ($p<0.0001$). The mean reduction from baseline in body weight for POMC deficiency obesity patients was -25.4 percent ($p<0.0001$), and the mean reduction from baseline in most hunger rating for POMC deficiency obesity patients was -27.8 percent ($p=0.0005$). In addition, 50 percent of the POMC deficiency obesity patients in the trial met or exceeded a 25 percent improvement in self-reported hunger scores ($p=0.0004$). Mean weight loss for these patients was 31.9 kg, or 70.2 pounds, over one year on therapy.

Summary of Efficacy Endpoints	POMC
Primary: Proportion of Participants Achieving at Least 10% Change in Body Weight[i]	80% ($p<0.0001$)
Key Secondary: Mean Percent Reduction from Baseline in Body Weight[ii]	-25.4% 90% CI: -28.80, -21.98 ($p<0.0001$)
Key Secondary: Mean Percent Reduction from Baseline in Most Hunger Rating[ii]	-27.8% 90% CI: -40.58, -14.96 ($p=0.0005$)
Key Secondary: Proportion of Participants with 25% Reduction in Hunger[iii]	50% ($p=0.0004$)

Five of 11 patients with LEPR deficiency obesity achieved the primary endpoint of greater than 10 percent weight loss over one year (p=0.0001). The mean reduction from baseline in body weight for LEPR deficiency obesity patients was -12.5 percent (p<0.0001), and the mean reduction from baseline in most hunger rating for LEPR deficiency obesity patients was -41.9 percent (p<0.0001). In addition, 72.7 percent of the LEPR deficiency obesity patients in the trial met or exceeded a 25 percent improvement in self-reported hunger scores (p<0.0001). Mean weight loss for these patients was 16.7 kg, or 36.8 pounds, over one year on therapy.

Summary of Efficacy Endpoints	LEPR
Primary: Proportion of Participants Achieving at Least 10% Change in Body Weight[i]	45.5% (p=0.0001)
Key Secondary: Mean Percent Reduction from Baseline in Body Weight[ii]	-12.5% 90% CI: -16.10, -8.83 (p<0.0001)
Key Secondary: Mean Percent Reduction from Baseline in Most Hunger Rating[ii]	-41.9% 90% CI: -54.76, -29.09 (p<0.0001)
Key Secondary: Proportion of Participants with 25% Reduction in Hunger[iii]	72.7% (p<0.0001)

In addition, the study design included a four-week placebo withdrawal period to further illustrate the effect of treatment with setmelanotide. Upon entry into the placebo period, participants almost immediately gained weight and experienced an increase in hunger, reversing their downward trends in weight loss and hunger scores observed during the first 12 weeks of the treatment period. In both trials, the mean weight increase during the four-week placebo period was approximately 5 kg, or more than 11 pounds, and this weight gain was accompanied by a worsening in hunger scores. These trends reversed again when patients went back on drug.

Consistent with prior clinical experience, setmelanotide was generally well-tolerated in both trials:

- Treatment-emergent related adverse events (AEs) included injection site reactions, nausea and vomiting, and increased hyperpigmentation (darkening of the skin); these were consistent with prior clinical trials of setmelanotide.
- There were no reports of cardiovascular AEs related to setmelanotide.
- One LEPR study patient withdrew before the end of titration due to AE of mild hypereosinophilia.
- There were no serious adverse events (SAEs) related to treatment with setmelanotide.
- One LEPR study patient died from injuries unrelated to the study drug. This patient was a passenger in a vehicle in a car accident and died from injuries from the accident.

“Setmelanotide demonstrated a clinically meaningful impact on severe hunger and obesity with 17 of 19 eligible patients choosing to participate in the extension study to continue setmelanotide treatment,” said Murray Stewart, M.D., Chief Medical Officer of Rhythm Pharmaceuticals. “Importantly, during withdrawal periods in both studies, patients experienced statistically significant, consistent increases in weight and hunger. Following re-initiation of therapy, the majority of patients resumed weight loss and hunger response. We believe these data speak to setmelanotide’s potential to help restore the function of the MC4R pathway in regulating weight and appetite control.”

Rhythm is on track to complete submission of a rolling New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) that will cover both POMC and LEPR deficiency obesities late in the fourth quarter of 2019 or the first quarter of 2020. Rhythm intends to request priority review of the application, which, if granted, could result in a six-month review process. Additionally, Rhythm also expects to submit a Marketing Authorization Application (MAA) with the European Medicines Agency (EMA), which will cover both POMC and LEPR deficiency obesities.

“For people living with genetically-driven, severe obesity and insatiable hunger, these pivotal data illustrate the potential of an effective therapy,” said Peter Kühnen, M.D., Institute for Experimental Pediatric Endocrinology, Charité Universitätsmedizin Berlin, Germany, lead investigator in the POMC deficiency obesity trial. “Recognizing the signs of rare genetic disorders of obesity early may soon open new possibilities with treatment options on the horizon.”

Rhythm anticipates sharing the full data from these Phase 3 clinical trials in POMC and LEPR deficiency obesities in a forthcoming publication and at a presentation at an upcoming medical meeting.

About Pivotal Phase 3 Trials in POMC and LEPR Deficiency Obesities

Rhythm's Phase 3 pivotal trials were designed in consultation with the FDA under Breakthrough Therapy status. Both trials are multicenter, open-label, single-arm trials that evaluated the efficacy and safety of setmelanotide for approximately one year in participants with either POMC or LEPR deficiency obesity who were 6 years of age and older.

Following screening and dose titration, participants received 12 weeks of therapeutic dose. There was also an eight-week blinded, drug withdrawal phase incorporated to further illustrate the effect of the drug. Lastly, participants received 32 weeks of therapeutic dose to complete approximately one year of treatment, before becoming eligible for the extension portion of the trial.

The primary endpoint in both studies assessed the percentage of participants who reached at least 10 percent weight loss as compared to historical controls in this population using an exact binomial comparison. Based on natural history data, it would be expected that no participant would be a responder over the course of a year. To be conservative, a comparator of 5 percent of patients who could have lost 10 percent weight or more without treatment was used.

The first two key secondary endpoints were the mean percent reduction from baseline of body weight and most hunger rating. The third key secondary endpoint was a hunger score responder analysis comparing the proportion of patients who achieved at least a 25 percent reduction in hunger score.

In each study, all patients were included in the evaluation for the primary endpoint, the weight responder analysis. All patients were also included for the hunger responder analysis. For the other two key secondary endpoints, mean percent reductions in weight and hunger, participants were included in the evaluation if by week 12 they achieved 5 kg of weight loss.[iv] Nine POMC and seven LEPR patients were included in these groups.

Rhythm expects to continue to enroll supplemental patients in both the POMC and LEPR deficiency obesities Phase 3 trials, primarily focusing on pediatric patients between 6-11 years of age.

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. The conference call may be accessed by dialing (844) 498-0570 (domestic) and (409) 983-9726 (international) and referring to conference ID 9775059. 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 Rare Genetic Disorders of Obesity

Rare genetic disorders of obesity are characterized by severe, early-onset obesity and insatiable hunger known as hyperphagia. The MC4R pathway is a key part of the biological process responsible for regulating hunger and body weight. Variants in many different genes within the MC4R pathway are associated with several rare genetic disorders of obesity. POMC deficiency obesity is a disorder caused by variants in the POMC or PCSK1 genes that can often lead to severe obesity beginning early in life, insatiable hunger, endocrine abnormalities, including adrenocorticotropic hormone deficiency and mild hypothyroidism, red hair and light skin pigmentation. LEPR deficiency obesity is a disorder caused by variants in the LEPR gene that can often lead to severe obesity beginning early in life, insatiable hunger, and endocrine abnormalities, including hypogonadotropic hypogonadism and hypothyroidism.

About Setmelanotide

Setmelanotide is a potent 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, Bardet-Biedl syndrome 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 MC4R agonist, in Phase 3 studies in patients with Pro-opiomelanocortin (POMC) deficiency obesity, Leptin receptor (LEPR) deficiency obesity, Bardet-Biedl syndrome, and Alström syndrome. The company is leveraging the Rhythm Engine -- comprised of its Phase 2 basket study, TEMPO Registry, GO-ID genotyping study and Uncovering Rare Obesity program -- to improve the understanding, diagnosis and potentially the treatment of rare genetic disorders of obesity. 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 for 2019 and 2020, estimated addressable patient populations, anticipated timing for enrollment, design and completion of clinical trials, the results of clinical trials, the FDA's or EMA's review of those results, the timing for filing of an NDA, the release of results of clinical trials, and Rhythm's strategy, prospects and plans. Statements using word such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward looking statements. Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions and uncertainties. Any or all of the forward-looking statements may turn out to be wrong, or be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Our statements about the results and conduct of our clinical trial could be affected by the potential that there are changes in the data or interpretation of the data by the FDA or EMA, whether the results will be deemed satisfactory by the FDA or EMA (for example, we describe the results of the trial as positive and the FDA or EMA may disagree with that characterization), and whether additional studies will be required or other issues will arise that will delay submission of our NDA or negatively impact acceptance, review and approval of setmelanotide by the FDA or EMA; and our statements about the potential commercial opportunity could be affected by the potential that our product does not receive regulatory approval, does not receive reimbursement by third party payors, or a commercial market for the product does not develop because of any of the risks inherent in the commercialization of pharmaceutical products. For all these reasons, actual results and developments could be materially different from those expressed in or implied by our forward-looking statements. All forward looking statements are subject to risks detailed in our filings with the U.S. Securities and Exchange Commission, including the Company's Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q. You are cautioned not to place undue reliance on these forward-looking statements, which are made only as of the date of this press release. We undertake no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstances.

[i] Exact binomial test assessing whether proportion of responders after one year of treatment would be greater than a conservative comparator of 5 percent of patients achieving up to 10 percent body weight loss over one year without setmelanotide.
[ii] Endpoint analyzed on evaluable population, which includes participants who are at least 12 years of age who also achieved weight loss threshold (5kg or 5 percent if <100 kg) after 12 weeks.
[iii] Score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for patients at least 12 years of age.
[iv] Or 5 percent weight loss if their baseline weight was less than 100 kg.

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