



Rhythm Pharmaceuticals Announces Late-breaking Data from Phase 3 Trials of Setmelanotide in POMC and LEPR Deficiency Obesities at ObesityWeek 2019

November 4, 2019

-- Data show treatment effect of setmelanotide on additional secondary endpoints, including body mass index --

-- Additional safety analyses show no significant increases in heart rate or blood pressure --

-- Two oral presentations delivered today during special research forum; poster presentations scheduled for Thursday --

BOSTON, Nov. 04, 2019 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq:RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic disorders of obesity, today announced additional data from its two pivotal Phase 3 clinical trials evaluating setmelanotide for the treatment of pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity showing the effect of setmelanotide on body mass index (BMI) scores and certain cardiovascular parameters. These data are being presented by study investigators in a special, late-breaking research forum during the 37th Annual Meeting of The Obesity Society at ObesityWeek[®] 2019, held November 3-7, 2019 in Las Vegas.

[In August 2019](#), Rhythm announced that both Phase 3 clinical trials of setmelanotide 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 deficiency obesity and LEPR deficiency obesity over the course of one year on setmelanotide treatment. Data from both trials also show that when patients withdrew from setmelanotide during a four-week placebo withdrawal period, they experienced rapid increases in weight and hunger. Setmelanotide is a melanocortin-4 receptor (MC4R) agonist designed to target impairments in the central melanocortin pathway, which is known to regulate weight and hunger.

"Setmelanotide has demonstrated a statistically significant and clinically meaningful impact on the severe obesity and unrelenting hunger in patients living with POMC deficiency obesity or LEPR deficiency obesity," said Murray Stewart, M.D., Chief Medical Officer of Rhythm Pharmaceuticals. "With these supporting data, we are also demonstrating that setmelanotide may have additional therapeutic benefits, driving improvements in BMI and other parameters that are critical to overall health. We are excited to present these data during ObesityWeek, where we are also collaborating with obesity experts to raise awareness of the unmet needs among people living with rare genetic disorders of obesity and to attempt to change the treatment paradigm to support patient identification and earlier diagnosis."

This week's presentations include new data showing the effect of setmelanotide on BMI scores for patients older than 19 and BMI z-scores for patients younger than 19, and its effect on vital signs including diastolic blood pressure, systolic blood pressure and heart rate. Additional analyses of safety data from the Phase 3 trials in POMC deficiency obesity and and LEPR deficiency obesity continue to support that setmelanotide is generally well-tolerated.

ObesityWeek Oral Presentations

Efficacy and Safety of the MC4R Agonist Setmelanotide in POMC Deficiency Obesity: A Phase 3 Trial

Peter Kühnen, M.D., Institute for Experimental Pediatric Endocrinology, Charité Universitätsmedizin Berlin, Germany, presented data from Rhythm's Phase 3 POMC deficiency obesity trial.

"Like many people living with rare genetic disorders of obesity, people with POMC deficiency obesity experience early-onset, rapid weight gain and severe, insatiable hunger, which are the two hallmarks of these disorders," said Dr. Kühnen, the lead investigator for this trial. "Despite significant effort to control their weight and appetite, such as supportive care or lifestyle interventions, patients often regain weight after any short-term period of weight loss. By reducing the weight gain and hunger endemic to POMC deficiency obesity, setmelanotide has the potential to shift the treatment paradigm for these patients."

Setmelanotide was associated with reductions in BMI and BMI z-scores¹ for patients with POMC deficiency obesity who were treated with setmelanotide for over one year at therapeutic dose:

POMC deficiency obesity

Baseline	~1 year at therapeutic	Percent change from
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	dose		baseline
Participants aged ≥19 years, mean (SD) BMI, kg/m ² (n=4)	43.90 (8.91)	34.58 (12.42)	-22.33 (14.75) P=0.056
Participants aged <19 years, mean (SD) BMI z-score (n=6)	3.35 (0.61)	1.73 (1.04)	-49.18 (27.20) P=0.007

Consistent with prior clinical experience, setmelanotide was well tolerated in patients with POMC deficiency obesity. There were no reported cardiovascular adverse events (AEs) related to setmelanotide, and no AEs or serious AEs that led to treatment discontinuation or death. Setmelanotide was not associated with significant changes to blood pressure or heart rate:

Mean parameter (SD) ²	Diastolic blood pressure (mmHg) ³	Systolic blood pressure (mmHg)	Heart rate (beats/min)
Baseline	73.13 (10.75)	111.57 (7.78)	81.03 (12.08)
~1 year at therapeutic dose	71.50 (9.17)	109.83 (6.12)	75.37 (7.25)
Percent change from baseline, %	-1.81 (6.27)	-1.36 (5.10)	-5.85 (11.44)
P value	P=0.38	P=0.42	P=0.14

Efficacy and Safety of the MC4R Agonist Setmelanotide in LEPR Deficiency Obesity: A Phase 3 Trial

Erica Van Den Akker, M.D., Ph.D., Erasmus MC-Sophia Children's Hospital University in Rotterdam, Netherlands, presented data from Rhythm's Phase 3 LEPR deficiency obesity trial.

"Broadly, we saw clinically meaningful, significant weight loss in patients with LEPR deficiency obesity in the Phase 3 trial. Notably, after over a year on therapeutic dose of setmelanotide, two patients experienced roughly fifteen percent weight loss, while two other patients showed greater than twenty percent weight loss," said Dr. Van Den Akker, lead investigator in the LEPR deficiency obesity trial. "Weight loss of this magnitude is unprecedented in the natural history of this patient population, and strongly suggests that setmelanotide has the potential to restore MC4R pathway function and serve as a safe, effective therapy for patients with rare genetic disorders of obesity."

Setmelanotide was associated with reductions in BMI and BMI z-scores⁴ for patients with LEPR deficiency obesity who were treated with setmelanotide for over one year at therapeutic dose:

LEPR deficiency obesity

	Baseline	~1 year at therapeutic dose	Percent change from baseline
Participants aged ≥19 years, mean (SD) BMI, kg/m ² (n=8)	51.18 (10.67)	45.82 (11.48) ⁵	-10.59 (8.11) P=0.01
Participants aged <19 years, mean (SD) BMI z-score (n=3)	3.52 (0.36)	3.03 (0.08)	-13.35 (8.87) P=0.12

Consistent with prior clinical experience, setmelanotide was well tolerated in patients with LEPR deficiency obesity. One participant discontinued therapy due to mild, treatment-related hypereosinophilia and one participant died from injuries as a passenger in a car accident, which was unrelated to the study drug. There were no reported cardiovascular AEs related to setmelanotide, and setmelanotide was not associated with significant changes in blood pressure or heart rate:

Mean parameter (SD) ⁶	Diastolic blood pressure (mmHg)	Systolic blood pressure (mmHg)	Heart rate (beats/min)
Baseline	67.67 (5.83)	121.697 (8.84)	79.46 (12.60)
~1 year at therapeutic dose	66.48 (8.59)	115.111 (14.57)	77.89 (16.46)
Percent change from baseline, %	-1.58 (13.038)	-3.78 (9.94)	-1.32 (15.46)
P value	P=0.73	P=0.29	P=0.80

Poster Presentations

Rhythm will present additional data on glucose and lipid parameters from the Phase 3 trials in POMC and LEPR deficiency obesities at ObesityWeek during the Pharmacotherapy Late Breaking Poster Session on Thursday, Nov. 7, from 12 noon - 1:30 p.m. PT (3 p.m. - 4:30 p.m. ET) in Mandalay Bay's Shoreline Exhibit Hall.

In addition, a third poster, "Functional Characterization of Missense Variants in LEPR, POMC, & PCSK1 Genes Arising From Single Nucleotide Variant (SNV)," will be presented during the CNS Poster Session on Tuesday, Nov. 5, 12 noon - 1:30 p.m. PT (3 p.m. - 4:30 p.m. ET), in the Shoreline Exhibit Hall.

Rhythm is on track to complete submission of a rolling New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for POMC deficiency obesity and LEPR deficiency obesity in the fourth quarter of 2019 or the first quarter of 2020, and the

Company expects to share additional data in forthcoming publications and medical meeting presentations.

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

Rhythm is a biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic disorders of obesity. In addition to POMC deficiency obesity and LEPR deficiency obesity, Rhythm also is evaluating setmelanotide in a pivotal Phase 3 study in patients with Bardet-Biedl syndrome and Alström syndrome, and expects to complete enrollment in the second half of 2019. 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 anticipated timing for enrollment of patients in clinical trials and submission of an NDA, its expectations regarding the impact of setmelanotide on BMI, heart rate, and blood pressure, its ongoing efforts related the efficacy of setmelanotide in patients with POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl syndrome and Alström syndrome,. 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 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 BMI z-score, or BMI standard deviation scores, are measures of relative weight adjusted for child age and sex.

² N=10 for all POMC vital signs

³ mmHG, millimeter of mercury

⁴ BMI z-score, or BMI standard deviation scores, are measures of relative weight adjusted for child age and sex.

⁵ N=7; one participant discontinued due to treatment-related adverse event.

⁶ N=9 for all LEPR vital signs



Source: Rhythm Pharmaceuticals, Inc.