Rhythm Pharmaceuticals Announces New Topline Clinical Data from Ongoing Phase 2 Basket Studies Evaluating Setmelanotide in Rare Genetic Disorders of Obesity

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-- Further Improvements Observed in Bardet-Biedl Syndrome Patients; Initial Proof-of-Concept Data in Alström Syndrome Demonstrates Significant Weight Loss and Decreased Hunger --
-- Rhythm Plans to Initiate Combined Pivotal Phase 3 Trial in Bardet-Biedl Syndrome and Alström Syndrome in 2018 --
-- Preliminary Data in Patients with POMC and Other MC4 Pathway Heterozygous Deficiency Obesities and POMC Epigenetic Disorders Demonstrate Clinically-Meaningful Reductions in Weight and Hunger --

BOSTON, June 18, 2018 (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 new topline clinical data from its ongoing Phase 2 basket studies of setmelanotide, a first-in-class melanocortin-4 receptor (MC4R) agonist, including updated data in patients with Bardet-Biedl Syndrome (BBS), initial proof-of-concept data in Alström Syndrome, and promising, preliminary data in pro-opiomelanocortin (POMC) and other MC4 pathway heterozygous deficiency obesities, as well as in POMC epigenetic disorders. Across all these rare genetic disorders of obesity, setmelanotide was observed to be well-tolerated.

“Despite growing awareness around rare genetic disorders of obesity, people living with these conditions are underserved by currently available treatments, which have limited efficacy and fail to address underlying disease biology,” said Robert M. Haws, M.D., Medical Director of Clinical Research at the Marshfield Clinic Research Foundation and an investigator in the study. “I, along with my other research collaborators, continue to study setmelanotide’s ability to curb excess hunger and reverse early-onset obesity, and we are encouraged by the updated data in BBS announced today. We are eager to continue studying the use of setmelanotide in a Phase 3 trial in BBS and Alström Syndrome.”

“These new clinical data build upon prior clinical experience and reinforce our confidence in setmelanotide as a potentially transformative treatment option,” said Keith Gottesdiener, M.D., Chief Executive Officer of Rhythm Pharmaceuticals. “With these results in hand, we are advancing our broad clinical development program for setmelanotide with optimism. We are particularly pleased to progress setmelanotide into a combined Phase 3 program in BBS and Alström Syndrome, which joins our fully-enrolled POMC and leptin receptor (LEPR) deficiency obesity trials as our third pivotal-stage trial. Based on recent interactions with the U.S. Food and Drug Administration (FDA), we have guidance for a combined trial in BBS and Alström Syndrome. This will enable us to evaluate setmelanotide simultaneously in these two rare genetic disorders of obesity that we believe share a similar pathophysiology and clinical presentation, which could potentially enable a more rapid path to regulatory filing. We also plan to enroll additional patients with POMC and other MC4 pathway heterozygous deficiency obesities, as well as POMC epigenetic disorders, in our ongoing Phase 2 basket studies in order to better understand the magnitude of setmelanotide’s effect and to inform our next steps.”

New Topline Clinical Data From Ongoing Phase 2 Basket Studies

Maturing Data Demonstrate Improved Efficacy in BBS:

- In October 2017, Rhythm announced proof-of-concept in BBS from five patients, on the basis of setmelanotide treatment lasting between 12-26 weeks. Since then, all four patients who were categorized as weight loss responders in the initial readout continue to lose weight, and after treatment duration of 46-60 weeks, patients achieved an average weight loss of 18.5% and an average hunger score decrease of 74.2%.
- As previously reported, the fifth patient, a pediatric patient with Type 1 diabetes, experienced a 53.3% decrease in hunger score, and an improvement in average blood sugar level from 10.1% to 7.6%. This patient did not experience any body weight change, though her weight curve indicated a slowing of prior childhood weight gain.
- An additional four patients with BBS were enrolled in the Phase 2 studies, all of whom have been on treatment for a short duration. Three of these patients remain on therapy. Two are already showing a promising response; the third patient is too early to determine. The fourth patient did not show improvements in either weight or hunger and was discontinued.
- Rhythm plans to present detailed results from its BBS Phase 2 studies at a major medical meeting later this year.

Proof-of-Concept Achieved in Alström Syndrome:

- The first patient experienced weight loss of 23.2% and a 45.5% decrease in hunger score after 38 weeks of treatment with

setmelanotide. As this patient's weight began approaching ideal body weight levels, a subsequent dose reduction was implemented, and this patient's weight stabilized.
- An additional three patients with Alström Syndrome were enrolled in the studies, all of whom have been on treatment for a short duration. Two of these patients remain on therapy; one is already showing a promising response, the other is too early to determine. The third patient did not show improvements in either weight or hunger and was discontinued.
- Rhythm plans to present detailed results from its Alström Syndrome Phase 2 studies at a major medical meeting later this year.

Initial Positive Results Observed in POMC and other MC4 Pathway Heterozygous Deficiency Obesities:

- Two patients responded to treatment with setmelanotide. The first patient experienced weight loss of 15.4% and a hunger score decrease of 80% and the second patient experienced weight loss of 6.5% and a hunger score decrease of 20%.
- Three additional patients with POMC and other MC4 pathway heterozygous deficiency obesities have been enrolled in the studies. One patient did not show improvements in either weight or hunger and was discontinued due to lack of efficacy, and two patients discontinued early due to tolerability issues related to muscle cramps or tanning, respectively.

Initial Positive Results Observed in POMC Epigenetic Disorders:

- The first patient with POMC epigenetic disorder obesity experienced a hunger score decrease of 60% during the titration phase, and began to lose weight. Over a four-week vacation during which she withdrew from treatment, the patient's hunger score returned to baseline, but her weight remained stable. After resuming treatment, this patient's hunger score again decreased and, over the course of the trial, she has experienced total weight loss of 9.2%.
- One additional POMC epigenetic patient has been enrolled in the studies and has been on treatment for a very short duration. This patient remains on therapy.

Consistent with prior clinical experience, treatment with setmelanotide was observed to be well-tolerated. The majority of adverse events reported by investigators were mild, primarily injection site reactions and increased skin pigmentation.

Clinical Development Plans for Setmelanotide in BBS and Alström Syndrome

Following recent discussions with the FDA, Rhythm plans to initiate a combined pivotal Phase 3 trial evaluating setmelanotide in patients with BBS and Alström Syndrome. Rhythm expects this open-label, single-arm, multinational trial to evaluate the safety and efficacy of setmelanotide in at least 20 BBS patients and at least six Alström Syndrome patients, aged six years and older, with setmelanotide administered once daily by subcutaneous injection for approximately 12 months. The trial will begin with an initial period of dose titration, using a simplified titration scheme. The trial may also include a 12-week, randomized, placebo-controlled period, after which all patients will complete an additional period of active setmelanotide treatment to complete the one-year trial.

Rhythm is continuing discussions with the FDA to finalize the trial design, protocol and endpoints, and expects to initiate the trial and enroll the first patients by the end of 2018.

Clinical Development Plans for Setmelanotide in POMC and other MC4 Pathway Heterozygous Deficiency Obesities and POMC Epigenetic Disorders

Rhythm intends to continue enrolling patients with POMC and other MC4 pathway heterozygous deficiency obesities, as well as POMC epigenetic disorders, in its ongoing Phase 2 basket studies, in order to identify those patients most likely to benefit from setmelanotide treatment.

The Company expects to announce updated data from a larger number of patients with POMC and other MC4 pathway heterozygous deficiency obesities, as well as POMC epigenetic disorders in the first quarter of 2019.

About Setmelanotide

Setmelanotide is a potent, first-in-class, melanocortin-4 receptor (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 U.S. Food and Drug Administration 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.

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 melanocortin-4 receptor (MC4R) agonist, in Phase 3 studies in patients with pro-opiomelanocortin (POMC) deficiency obesity (which includes deficiencies in both the POMC and PCSK1 genes) and leptin receptor (LEPR) deficiency obesity. Rhythm also supports The Genetic Obesity Project (www.GeneticObesity.com), which is dedicated to improving the understanding of severe

obesity that results from specific genetic disorders. 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 plans and timing regarding the design of patient enrollment and announcement of data from clinical trials, and potential regulatory filings, and related statements. Statements using words such as "expect", "anticipate", "believe", "may", "will", "plan", "goal" 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, the impact of changes in the financial markets and global economic conditions, risks associated with data analysis and reporting, our use of cash 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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