Rhythm Pharmaceuticals Announces Submission of Marketing Authorization Application to the European Medicines Agency for Setmelanotide in POMC and LEPR Deficiency Obesities

July 1, 2020

-- Company also announces positive data from eight supplemental patients, including four pediatric patients, enrolled in pivotal Phase 3 clinical trials; all achieved primary endpoint of 10 percent weight loss --

-- Setmelanotide was well-tolerated in long-term extension study with continued clinical benefit and durable weight loss observed at up to three years on therapy --

BOSTON, July 01, 2020 (GLOBE NEWSWIRE) -- Rhythm Pharmaceuticals, Inc. (Nasdaq:RYTM), a late-stage biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic disorders of obesity, today announced that it has submitted its Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for setmelanotide, the company's melanocortin-4 receptor (MC4R) agonist, for the treatment of pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity. The company has been granted accelerated assessment of the MAA, which potentially shortens review time by the Committee for Medicinal Products for Human Use (CHMP).

In conjunction with this submission, Rhythm announced additional positive data from eight supplemental patients, including four pediatric patients, enrolled in its two pivotal Phase 3 clinical trials for POMC and LEPR deficiency obesities, as well as updated data from its long-term extension study of setmelanotide in patients with POMC or LEPR deficiency obesity. Rhythm included these data in its MAA submission package to the EMA.

"We are pleased to have submitted our MAA for setmelanotide for the treatment of POMC and LEPR deficiency obesities, another step toward our goal of delivering setmelanotide to patients with these ultra-rare disorders," said Murray Stewart, M.D., Chief Medical Officer of Rhythm. "We are also excited to report additional data that provide further evidence regarding setmelanotide's potential impact in driving weight loss in patients with POMC or LEPR deficiency obesity. In particular, we are encouraged to see therapeutic activity in children and adolescents among our supplemental patients. These chronic disorders often arise in childhood, with patients suffering from severe obesity and insatiable hunger beginning at a very young age. By intervening earlier, we believe it may be possible to reduce body weight and hunger significantly, thereby preventing the development of debilitating comorbidities often associated with early-onset, rapid weight gain and improving quality of life for patients and their families."

Dr. Stewart continued, "Additionally, data from our extension study show that treatment with setmelanotide remained well-tolerated for upwards of three years, with patients continuing to maintain, or even deepen, their weight loss."

In August 2019, Rhythm announced positive topline results from the pivotal cohorts in its two Phase 3 clinical trials evaluating setmelanotide for the treatment of POMC and LEPR deficiency obesities. Both trials met their primary endpoints and all key secondary endpoints, demonstrating a statistically significant and clinically meaningful increase in weight loss and reductions in insatiable hunger, or hyperphagia, in patients with POMC and LEPR deficiency obesities.

Data on Supplemental Patients with POMC and LEPR Deficiency Obesities

Rhythm enrolled a total of eight patients, including four pediatric patients between the ages 6 and 12 years old, in supplemental cohorts in its Phase 3 trials evaluating setmelanotide for the treatment of POMC deficiency obesity and LEPR deficiency obesity, with four supplemental patients enrolled in each trial. All eight supplemental patients achieved the primary endpoint of 10 percent or greater weight loss at 52 weeks on setmelanotide therapy, as calculated under the same statistical analysis plan used in the pivotal trials. All of the supplemental patients were enrolled by European investigators, as were most of the patients in the pivotal cohorts.

The mean reduction in baseline body weight for the supplemental POMC deficiency obesity patients was -26.3 percent, and the mean reduction in body weight for the supplemental LEPR deficiency obesity patients was -13.2 percent. The estimated mean percentage reduction in most hunger score for evaluable patients in the supplemental cohorts was -57.3 percent. Hunger scores collected from children younger than 12 were calculated differently and therefore not counted in this analysis.

Combining data from the eight supplemental patients with data from the pivotal cohorts, 12 out of 14 patients with POMC deficiency obesity and 9 out of 15 patients with LEPR deficiency obesity achieved the primary endpoints of greater than 10 percent weight loss over approximately one year. Additionally, the data for all key secondary endpoints from the supplemental

cohorts were consistent with the data from the pivotal cohorts.

Long-term Extension Data for POMC and LEPR Deficiency Obesities

A total of 15 patients who participated in the pivotal studies are being treated in the extension study, including nine living with POMC deficiency obesity and six living with LEPR deficiency obesity, all of whom previously completed one of Rhythm's two pivotal Phase 3 trials evaluating setmelanotide for the treatment of severe obesity and insatiable hunger. Two additional patients who were enrolled in the LEPR deficiency obesity pivotal study are expected to enroll in the extension study, pending local regulatory approval, and one patient with POMC deficiency obesity enrolled in the pivotal study did not continue in the extension study.

As of April 16, 2020, extension study data show that patients successfully maintained durable weight loss with long-term treatment with setmelanotide for a total of up to 155 weeks. Hunger scores have typically remained stable throughout the extension study. Treatment in the extension study remains ongoing.

Safety

Consistent with prior clinical experience, setmelanotide has been was generally well-tolerated in the supplemental patient cohorts and in the long-term extension study. As of April 16, 2020, the safety results of setmelanotide remained consistent across all patients treated for up to three years. The most common treatment-emergent related adverse events (AEs) included injection site reactions, nausea and vomiting, and hyperpigmentation (darkening of the skin).

Rhythm is continuing to analyze the efficacy and safety data from both the supplemental cohorts and the ongoing long-term extension study, and it plans to share more of these data at an upcoming medical meeting.

About Setmelanotide
Setmelanotide is an investigational, melanocortin-4 receptor (MC4R) agonist. The MC4R is part of the key biological pathway that independently regulates energy expenditure and appetite. Variants in genes may impair the function of the MC4R pathway, potentially leading to insatiable hunger and early-onset, severe obesity. Rhythm is currently developing setmelanotide as a targeted therapy to potentially restore the function of an impaired MC4R pathway and, in so doing, potentially reduce hunger and weight in patients with rare genetic disorders of obesity. Currently, no pharmacologic therapies exist to treat these conditions. The FDA has granted Breakthrough Therapy designation to setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4R in the central melanocortin pathway, which includes pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity. The EMA 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. Both the FDA and EMA have granted orphan drug status to setmelanotide for POMC and LEPR deficiency obesities. The FDA has accepted Rhythm's NDA for setmelanotide for the treatment of POMC and LEPR deficiency obesities for filing, granted Priority Review of the NDA and assigned a Prescription Drug User Fee Act (PDUFA) goal date of November 27, 2020. Rhythm submitted a MAA for setmelanotide to treat individuals living with POMC deficiency obesity or LEPR deficiency obesity to the EMA in June 2020.

About Rhythm Pharmaceuticals
Rhythm is a late-stage biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic disorders of obesity. In August 2019, the company announced positive topline results from pivotal Phase 3 clinical trials of setmelanotide, its MC4R agonist, in people living with POMC deficiency obesity or LEPR deficiency obesity. In May 2020, the FDA accepted Rhythm's NDA for setmelanotide in POMC or LEPR deficiency obesity, and in June 2020 the company submitted a MAA to the EMA. Rhythm is also evaluating setmelanotide for reduction in hunger and body weight in a pivotal Phase 3 trial in people living with Bardet-Biedl and Alström syndromes, with topline data from this trial expected in the fourth quarter of 2020 or early in the first quarter of 2021. Rhythm 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 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, and regulatory and clinical progress of setmelanotide, anticipated trial enrollment and timing of data readouts, and our expectations surrounding the PDUFA goal date. Statements using words such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the impact of our management transition, 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 liquidity and expenses, the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2020 and our 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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