Rhythm Presents Positive Initial Data for Setmelanotide in LepR Deficiency Obesity

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– Significant weight loss with targeted treatment in a second rare genetic disorder affecting the MC4 weight regulation pathway –

BOSTON, November 4, 2016—Rhythm, a biopharmaceutical company developing peptide therapeutics for rare genetic deficiencies that result in life-threatening metabolic disorders, today announced the presentation of results from an ongoing Phase 2 clinical trial assessing the safety and efficacy of setmelanotide (RM-493), the company's novel melanocortin-4 receptor (MC4R) agonist, for the treatment of leptin receptor (LepR) deficiency obesity. The study was presented at the ObesityWeek 2016 conference in New Orleans in a poster presentation entitled, "Proof of Concept for Treatment of a Second Rare Genetic Disorder of the Leptin-Melanocortin Pathway: Successful Therapy of Extreme Obesity in a Leptin-Receptor (LepR) Deficient Patient with Setmelanotide."

The presentation reported initial data for the first patient enrolled in a Phase 2 non-randomized, open-label clinical trial of setmelanotide for the treatment of LepR deficiency obesity, a rare genetic disorder associated with severe, early-onset obesity and unrelenting hyperphagia that Rhythm estimates affects up to 2,000 people in the U.S. This investigator-initiated trial, conducted in collaboration with lead investigator Peter Kühnen, M.D., Institute for Experimental Pediatric Endocrinology, Charité Universitätsmedizin in Berlin, Germany, evaluated the safety and efficacy of setmelanotide administered once daily by subcutaneous injection. The presentation outlined results from the study in which the patient had substantial and sustainable reduction of hunger and weight:

- — With setmelanotide treatment, LepR Patient 1 lost 56.4 lbs. over 22 weeks, from a baseline weight of 288 lbs.—a 19.6% decrease.
- — Patient 1 experienced a substantial reduction in hunger from a baseline hunger score of 9 (using a Likert score 0-10, with 0 representing no hunger and 10 representing extreme hunger) to a score of 1-2, reversing his hyperphagia.
- — Setmelanotide was well tolerated, with no serious adverse events reported.

This initial efficacy data in a LepR deficiency patient provides a second proof-of-concept demonstration that setmelanotide has potential to provide meaningful efficacy in genetic forms of obesity due to MC4 pathway deficiency by restoring absent LepR-POMC signaling. Recently, *The New England Journal of Medicin*e reported results from a setmelanotide Phase 2 trial in pro-opiomelanocortin (POMC) deficiency obesity that demonstrated substantial weight loss in two adult patients.[1]

"The Leptin-MC4 pathway is the critical biological pathway that regulates weight," said Sadaf Farooqi, PhD, FRCP, FMedSci, University of Cambridge Metabolic Research Laboratories, and an investigator for the study. "This trial is very exciting because it further validates the opportunity to use setmelanotide as replacement therapy in genetic disorders that disrupt this important pathway."

"We are pleased to see these positive results with setmelanotide in LepR deficiency obesity, a second rare genetic disorder of the MC4 pathway," said Keith Gottesdiener, CEO of Rhythm. "On the strength of the initial data with setmelanotide, we are expanding the setmelanotide clinical program in coming months, targeting three additional MC4 pathway deficiencies. We have also launched The Genetic Obesity Project to support expanded genotyping and diagnosis of POMC and LepR deficiency obesity."

About LepR Deficiency Obesity
LepR deficiency obesity is an ultra-rare orphan disease resulting in extreme hyperphagia and severe early-onset obesity, with an estimated prevalence of 1% of subjects with severe, early-onset obesity. Rhythm estimates that actual prevalence could be between 500 and 2,000 patients in the U.S. Like other deficiencies upstream in the MC4 pathway, LepR deficiency results in loss of function in the MC4 pathway. Therefore, patients with this indication also manifest intense hyperphagia and severe obesity from early childhood. Currently, there is no approved treatment for the obesity and hyperphagia associated with LepR deficiency obesity.

About Setmelanotide (RM-493)
Setmelanotide is a potent, first-in-class MC4R agonist in development for the treatment of obesity caused by genetic deficiencies in the MC4 pathway, a key pathway in humans that regulates energy expenditure, homeostasis, and appetite. The critical role of the MC4 pathway in weight regulation was validated with the discovery that single genetic defects along this pathway result in early-onset and severe obesity. In addition to the Phase 2 trial for POMC and LepR deficiency, a second Phase 2 setmelanotide trial is ongoing for the treatment of Prader-Willi syndrome (PWS), a rare genetic disorder that causes unrelenting hyperphagia and life-threatening obesity. Recent scientific evidence implicates defects in the MC4 pathway as the likely cause of the weight and appetite abnormalities in PWS.

About The Genetic Obesity Project
The Genetic Obesity Project is dedicated to improving the understanding of severe obesity that is caused by specific genetic defects—particularly rare genetic disorders that result in life-threatening obesity. The Project has initiated a genotyping study and a patient registry, both focusing on identifying people with pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LepR) deficiency obesity. Study investigators are located in both the U.S. and EU. Healthcare providers can register patients to participate in the study at www.GeneticObesity.com.

About Rhythm (www.rhythmtx.com)
Rhythm is a biopharmaceutical company focused on developing peptide therapeutics for the treatment of rare genetic deficiencies that result in life-threatening metabolic disorders. Rhythm's lead peptide product candidate is setmelanotide, a first-in-class melanocortin 4 receptor (MC4R) agonist for the treatment of rare genetic disorders of obesity. Rhythm supports The Genetic Obesity Project (www.GeneticObesity.com), which is dedicated to improving the understanding of severe obesity that is caused by specific genetic defects. The company is based in Boston, Massachusetts.

1 Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, Mai K, Blume-Peytavi U, Grüters A, Krude H. "Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist." *N Engl J Med.* July 2016; 375:240-246.