Rhythm Receives Expanded FDA Breakthrough Therapy Designation for Setmelanotide for Rare Genetic Disorders of Obesity

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— New designation for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway —
— Expands upon previous designation for POMC deficiency obesity —

BOSTON, May 11, 2017—Rhythm today announced that the U.S. Food and Drug Administration (FDA) has expanded a previously granted Breakthrough Therapy Designation (BTD) for setmelanotide, the company's novel melanocortin-4 receptor (MC4R) agonist. The expanded BTD is for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway (the MC4 pathway), which includes both pro-opiomelanocortin (POMC) and leptin receptor (LepR) deficiency obesity. The FDA had previously granted BTD to setmelanotide for the treatment of POMC deficiency obesity.

Rhythm is developing setmelanotide for the treatment of obesity caused by genetic deficiencies in the MC4 pathway, a key biological pathway in humans that regulates weight by increasing energy expenditure and reducing appetite. The company has completed positive Phase 2 clinical trials in both POMC deficiency obesity and LepR deficiency obesity in which patients treated with setmelanotide experienced significant weight loss and substantial reductions in hunger. Setmelanotide was well tolerated in these trials. Rhythm recently initiated a Phase 3 clinical trial of setmelanotide in POMC deficiency obesity.

"We are developing setmelanotide to restore lost function in upstream MC4 pathway disorders for which there are no approved therapies," said Keith Gottesdiener, CEO of Rhythm. "We are grateful to receive this expanded Breakthrough Therapy Designation, and we look forward to continuing to work closely with the FDA to bring this therapy to patients living with these life-threatening genetic disorders of obesity."

The FDA grants BTD to expedite the development and review of therapeutics to treat serious or life-threatening conditions for which preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement on at least one clinically significant endpoint over existing therapies. This designation conveys all FDA Fast Track program features, such as eligibility for rolling new drug application (NDA) submissions and priority review (if supported by clinical data at the time of NDA). Additionally, this designation provides more intensive involvement of FDA staff in a proactive, collaborative, cross-disciplinary review process.

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 biological pathway in humans that regulates weight by increasing energy expenditure and reducing 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 2016, *The New England Journal of Medicine* reported results from a setmelanotide Phase 2 trial in POMC deficiency obesity that demonstrated substantial weight loss in two adult patients. At ObesityWeek 2016, investigators presented initial data for the first patient enrolled in a Phase 2, open-label clinical trial of setmelanotide for the treatment of LepR deficiency obesity. Both POMC and LepR deficiency obesity are rare genetic disorders associated with severe, early-onset obesity and unrelenting hyperphagia. The initial efficacy data with setmelanotide in these disorders demonstrate that setmelanotide has the potential to provide meaningful efficacy in genetic forms of obesity due to MC4 pathway deficiency by restoring absent LepR-POMC signaling. The company is currently evaluating setmelanotide for the treatment of the following genetic disorders of obesity: POMC deficiency obesity, LepR deficiency obesity, Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders. Rhythm recently initiated a Phase 3 clinical trial of setmelanotide in POMC deficiency obesity.

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 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.