Hyperphagia and Body Weight Gain Are Reduced With Once-Weekly Treatment With RM-718, a Selective Melanocortin-4 Receptor Agonist, in Zucker Obese Rats

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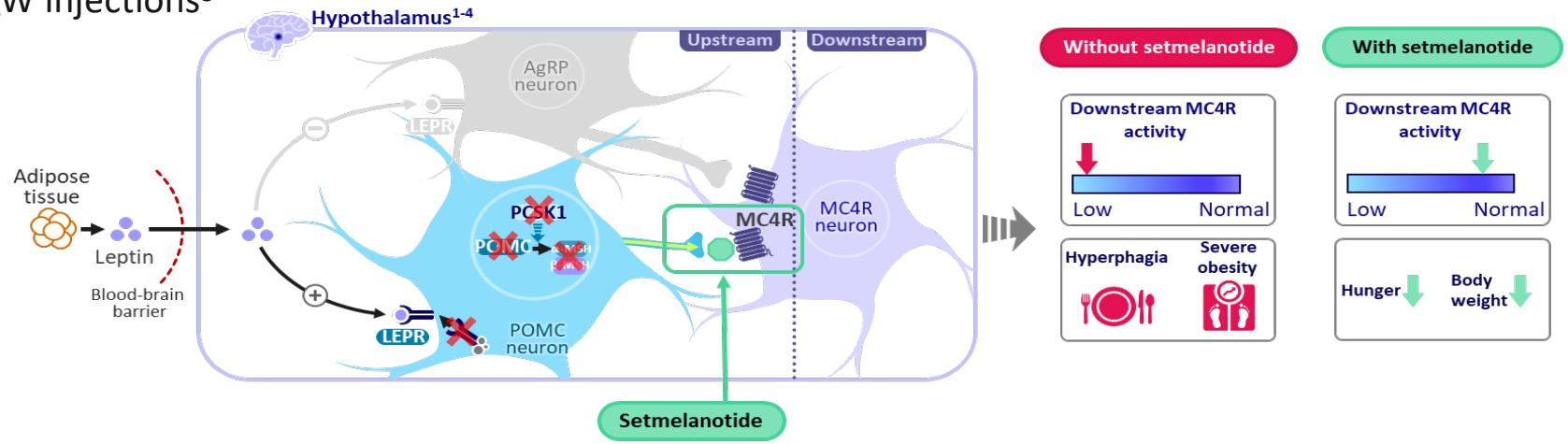
New Generation of a Selective MC4R agonist, RM-718

- Hypothalamic MC4R signaling regulates hunger, satiety, and energy expenditure; impairments in the MC4R pathway can cause hyperphagia and early- or rapid-onset, severe obesity[1-4]
- Setmelanotide, an MC4R agonist, reduces hunger and weight in patients with certain MC4R pathway impairments owing to POMC or LEPR deficiencies, Bardet-Biedl syndrome, and acquired hypothalamic obesity in clinical trials; however, treatment is associated with reversible skin hyperpigmentation due to residual MC1R activity[5-7]
- The highly selective (MC1R sparing) and potent synthetic, cyclic heptameric MC4R agonist RM-718 is a formulation for sustained release for QW injections[8]



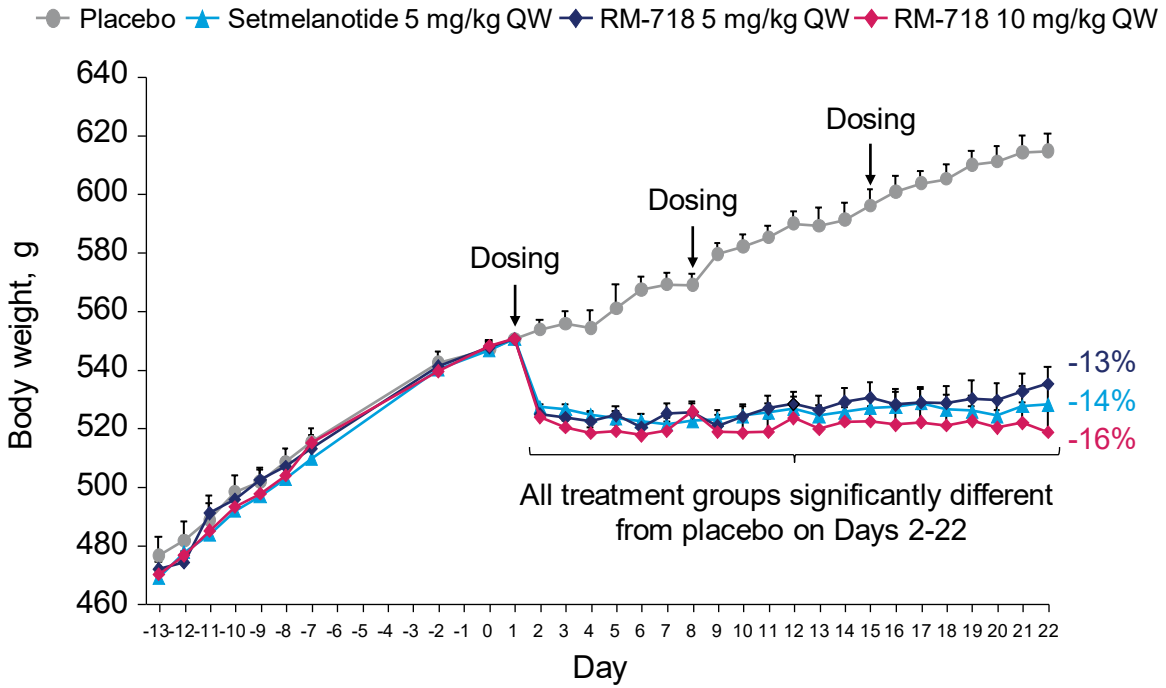
Objective: to test in vivo efficacy of RM-718 on hyperphagia and body weight in Zucker obese rats, a rodent model of genetic obesity caused by LEPR deficiency

AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; QW, once weekly. **1.** Abuzzahab et al. *Horm Res Paediatr*. 2019;91(2):128-136. **2.** Huvenne et al. *Obes Facts*. 2016;9(3):158-173. **3.** Dykens et al. *Obesity (Silver Spring)*. 2007;15(7):1816-1826. **4.** Heymsfield et al. *Obesity (Silver Spring)*. 2014;22(suppl 1):S1-S17. **5.** Roth et al. *Lancet Diabetes Endocrinol.* 2024;12:380-389. **6.** Clement et al. *Lancet Diabetes Endocrinol*. 2020;8(12):960-970. **7.** Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10(12):859-868. **8.** Data on file, Rhythm Pharmaceuticals, Inc.

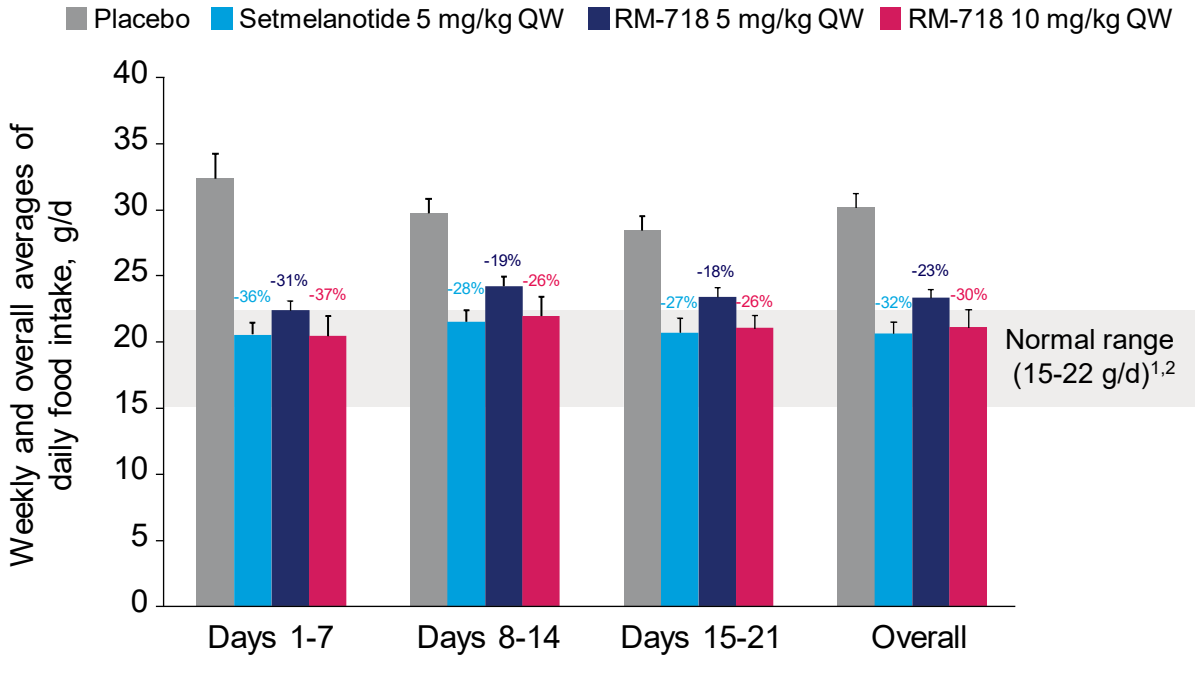
RM-718 Demonstrated Reduction in Body Weight and Food Intake

- 21-day parallel study of 4 arms (n=8): placebo, setmelanotide 5 mg/kg QW, RM-718 5 mg/kg QW, and RM-718 10 mg/kg QW

Body Weight



Normalization of Food Intake

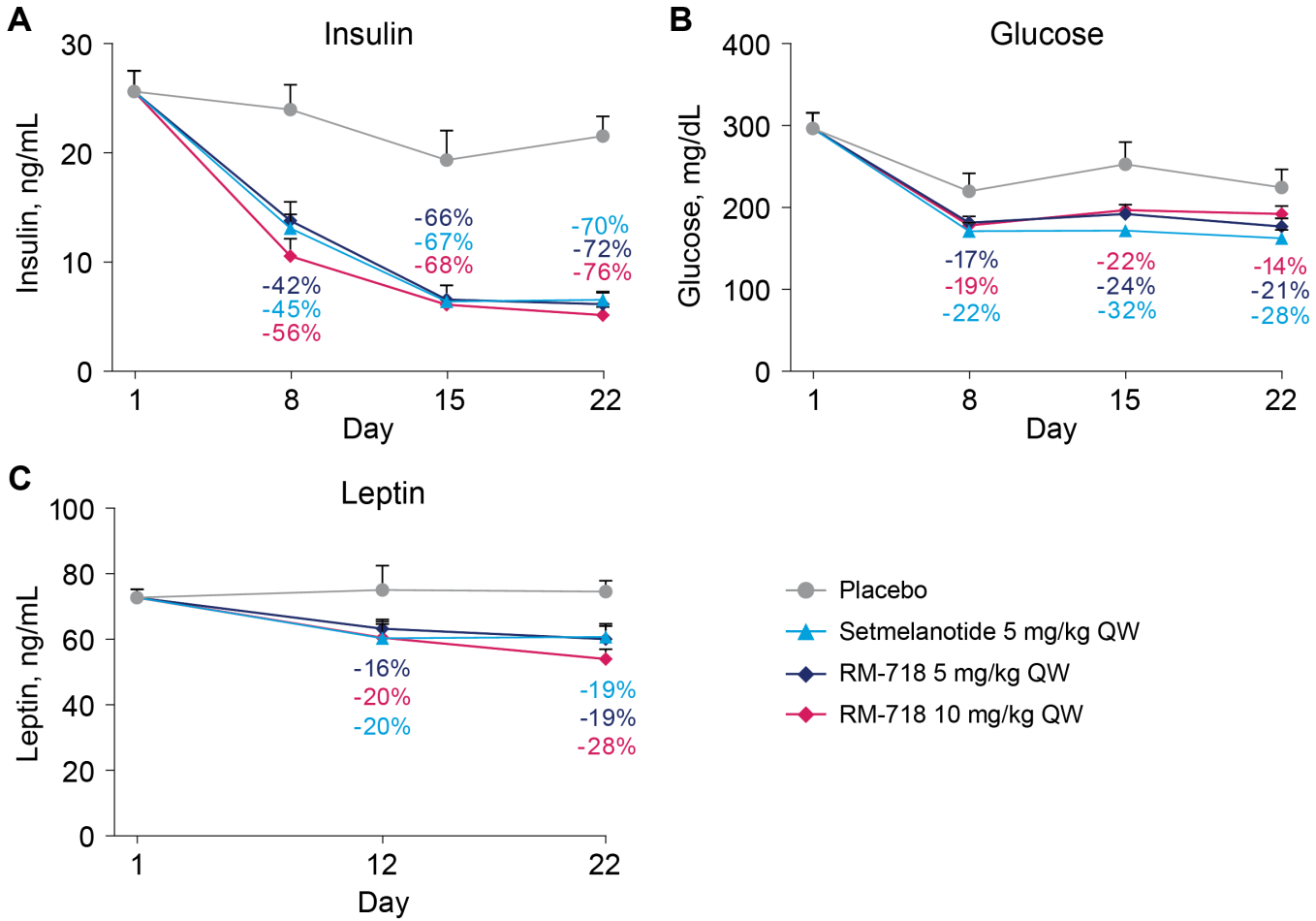


All treatment arms/time points had significantly reduced body weight and food intake versus placebo ($P<0.05$). Error bars represent standard error of the mean. QW, once weekly.

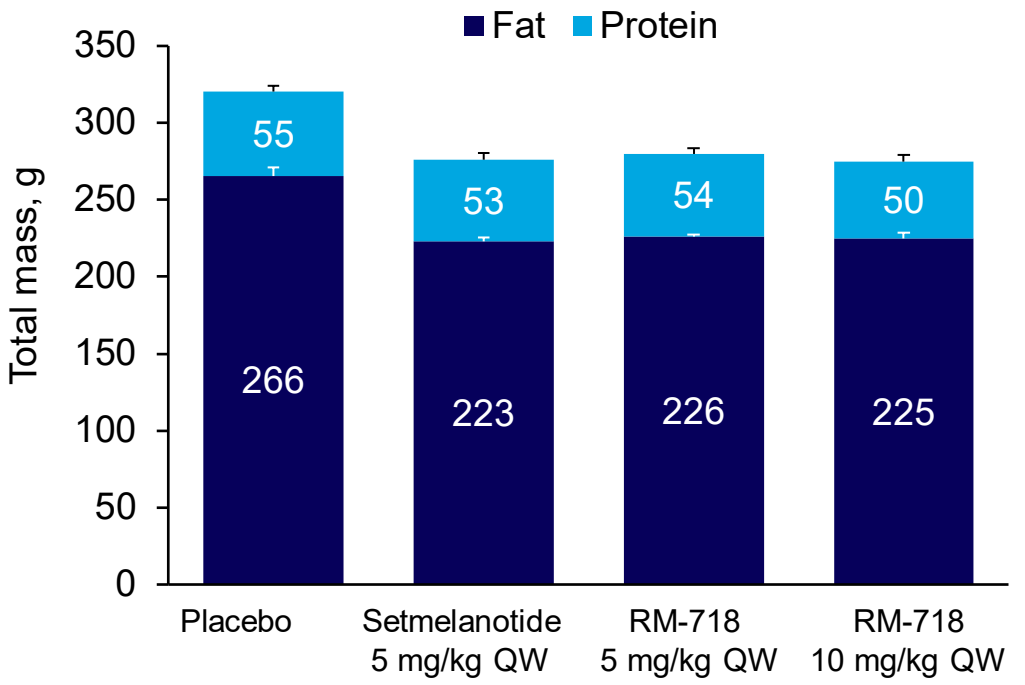
1. Fetissov and Meguid. *Nutrition*. 2020;70S:100011. **2.** Yu et al. *Sci Prog*. 2021;104(2):368504211009669.

RM-718 Reduces Insulin Levels and Fat Mass

Insulin Sensitivity Improvement



Carcass Fat and Protein Mass



Percent change vs placebo	Fat mass	−16*	−15*	−15*
	Protein mass	−4	−2	−8

Across all time points in all treatment groups, fasted plasma glucose and insulin were significantly reduced ($P<0.05$) or exhibited a trend of reduction from placebo.
QW, once weekly. Error bars represent standard error of the mean. *$P<0.001$ vs placebo.

Summary and Conclusions

- Three weeks of RM-718 QW was well tolerated and led to sustained reduction of hyperphagia, body weight, and fat mass with no changes in lean mass in Zucker obese rats; treatment also led to improved insulin sensitivity similar to that observed with setmelanotide
- A separate animal study in nonhuman primates demonstrated that RM-718 up to 30 mg/kg QW did not result in changes in heart rate or blood pressure, suggesting that, similar to setmelanotide, RM-718 does not produce off-target cardiovascular effects
- These data support the continued clinical evaluation of RM-718 as a highly specific MC4R agonist that is not expected to cause hyperpigmentation

A first-in-human, first-in-patient, Phase 1 trial of RM-718 QW in patients with general obesity or acquired hypothalamic obesity is underway, and the first patient was dosed in March 2024

The related study design will be presented on June 3 from 12:00 PM-1:30 PM (Poster 665)

MC4R, melanocortin-4 receptor; QW, once weekly.