A Pilot Study with the Synthetic Peptide Setmelanotide (RM-493), a Melanocortin-4 Receptor Agonist, for the Treatment of Heterozygous MC4R Deficiency Obesity

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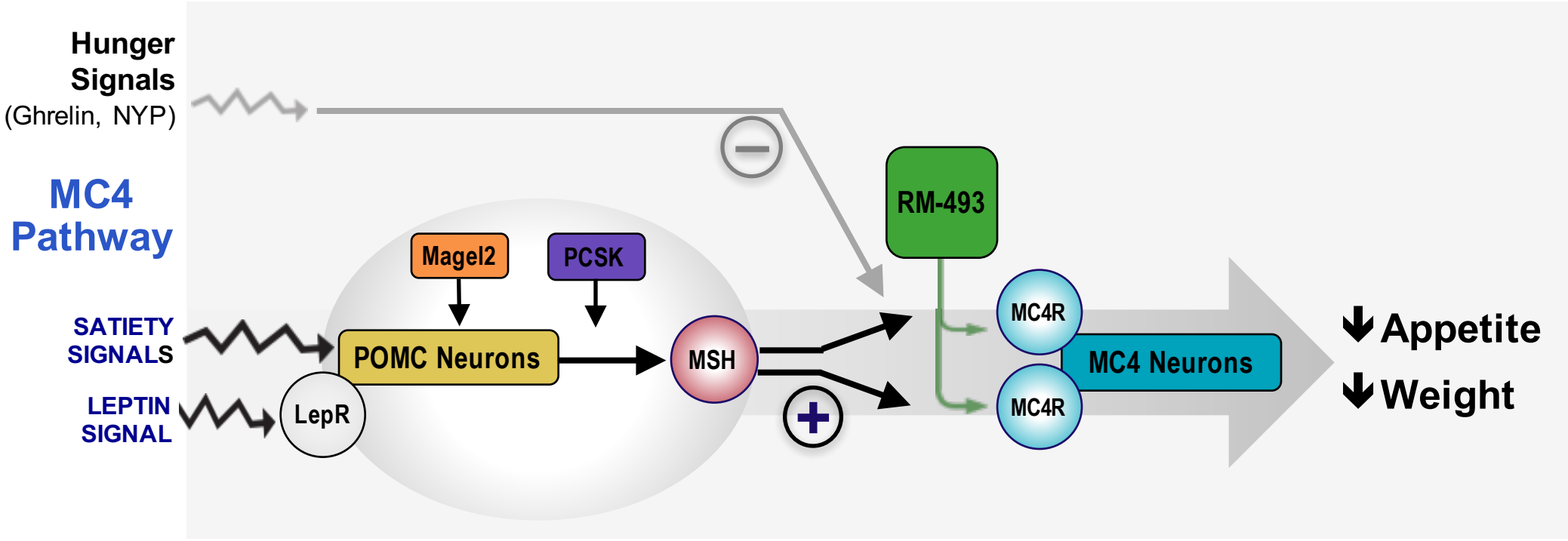
Setmelanotide (RM-493)

MC4R Agonist for Obesity due to Genetic Deficiencies in the MC4 Pathway

- Setmelanotide: 8 AA peptide with high potency (EC_{50} 0.27 nM)
- Large toxicological margins at the NOAEL (>300 fold)
- Weight Loss efficacy without BP changes in obese monkeys

Melanocortin-4 pathway

- **Key hypothalamic pathway that plays a critical role in the control of food intake and energy balance**



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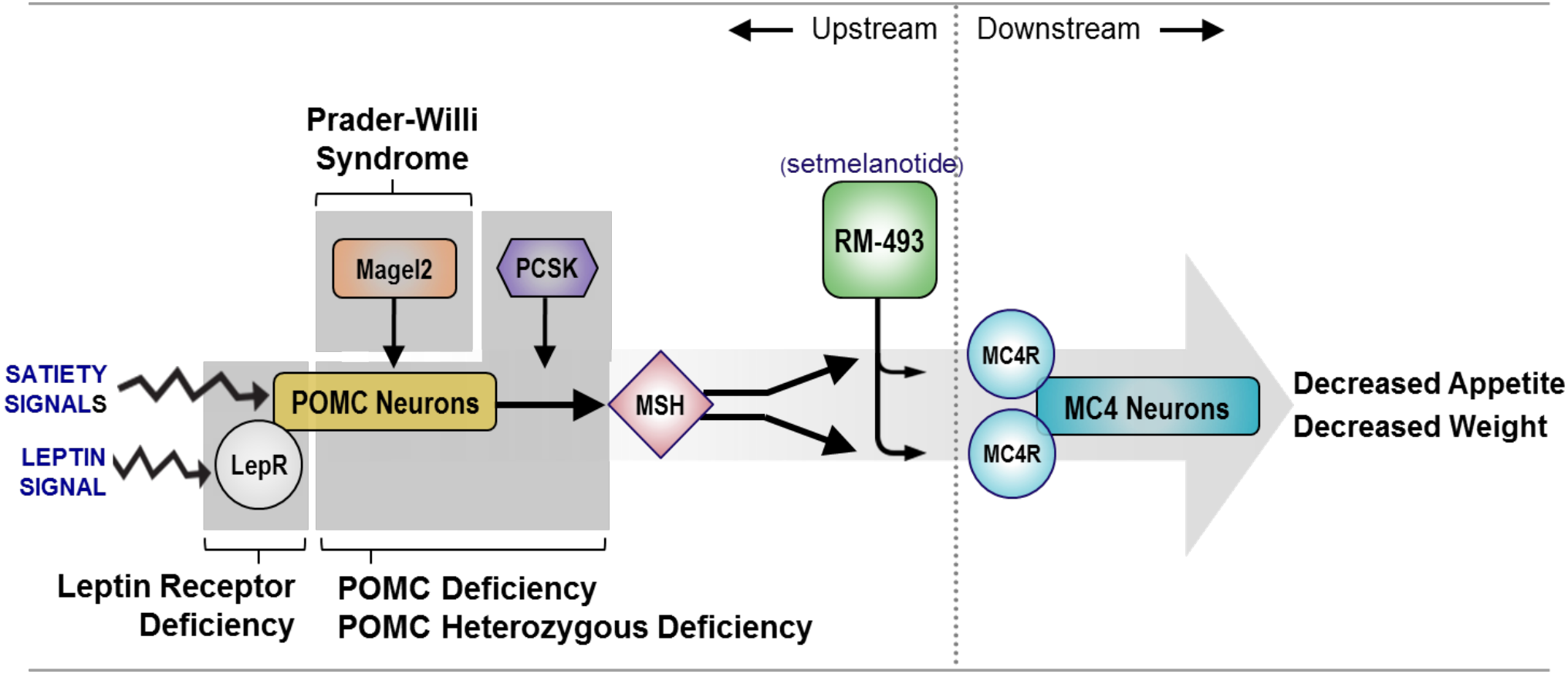
MC4R Agonist RM-493: Obesity due to Genetic Deficiencies in MC4 Pathway

"Upstream" Deficiencies"

MC4 pathway

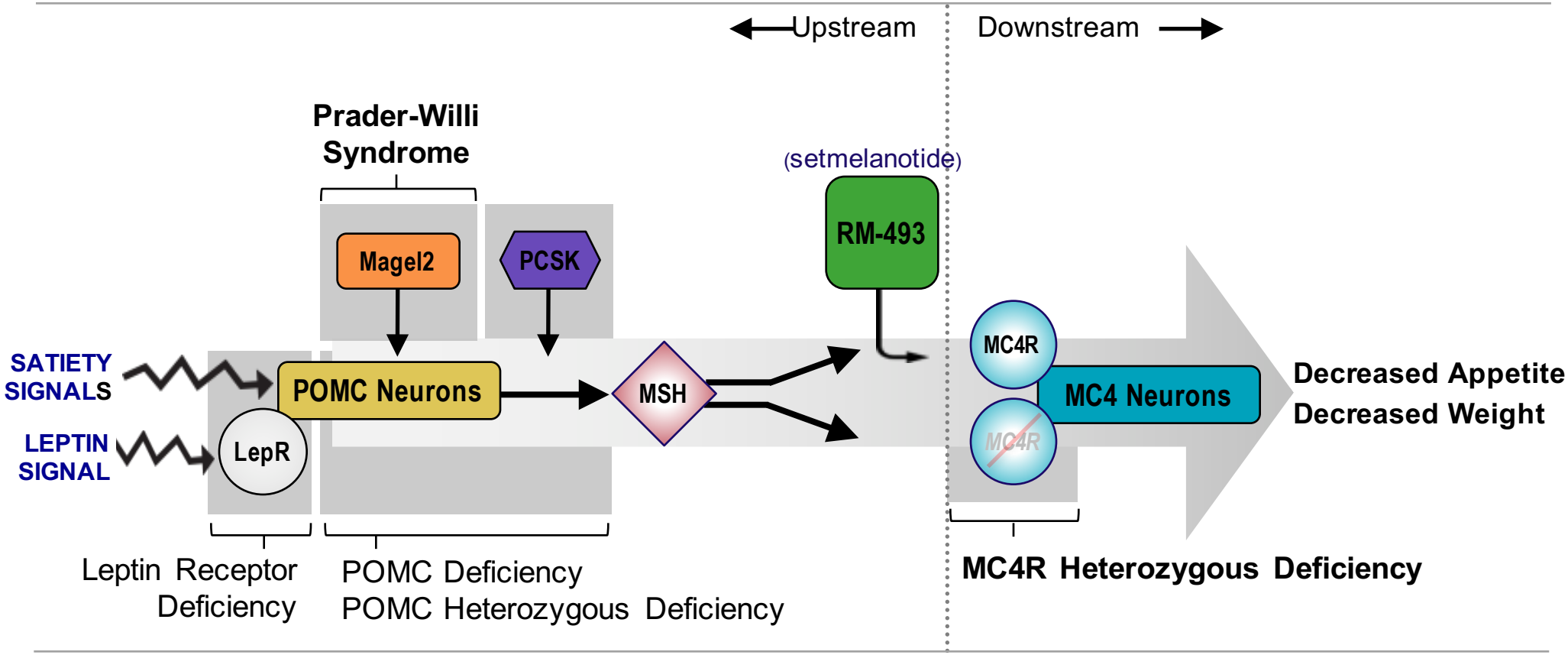


POMC deficiency includes both POMC gene deficiency and/or PCSK1 gene deficiency

MC4R Agonist RM-493: Obesity due to Genetic Deficiencies in MC4 Pathway

"Downstream" Deficiency

MC4 Pathway



Defects at the MC4 Receptor

MC4R Homozygous Loss of Function Variants

- Early, profound obesity and hyperphagia

MC4R Heterozygous Partial or Full Loss of Function Variants

- Most common monogenic cause of obesity
- Early and severe obesity
- Prevalence*: 1-3% of BMI>30 and up to 4% of BMI>35
- Approximately 1M US patients*
- Comprehensive analysis of MC4R variant functional analysis and MC4R variant clinical phenotypes is ongoing

*Rhythm estimates from published literature

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MC4R Heterozygous Deficiency Obesity: Phase Ib study

Study Design slide with variants

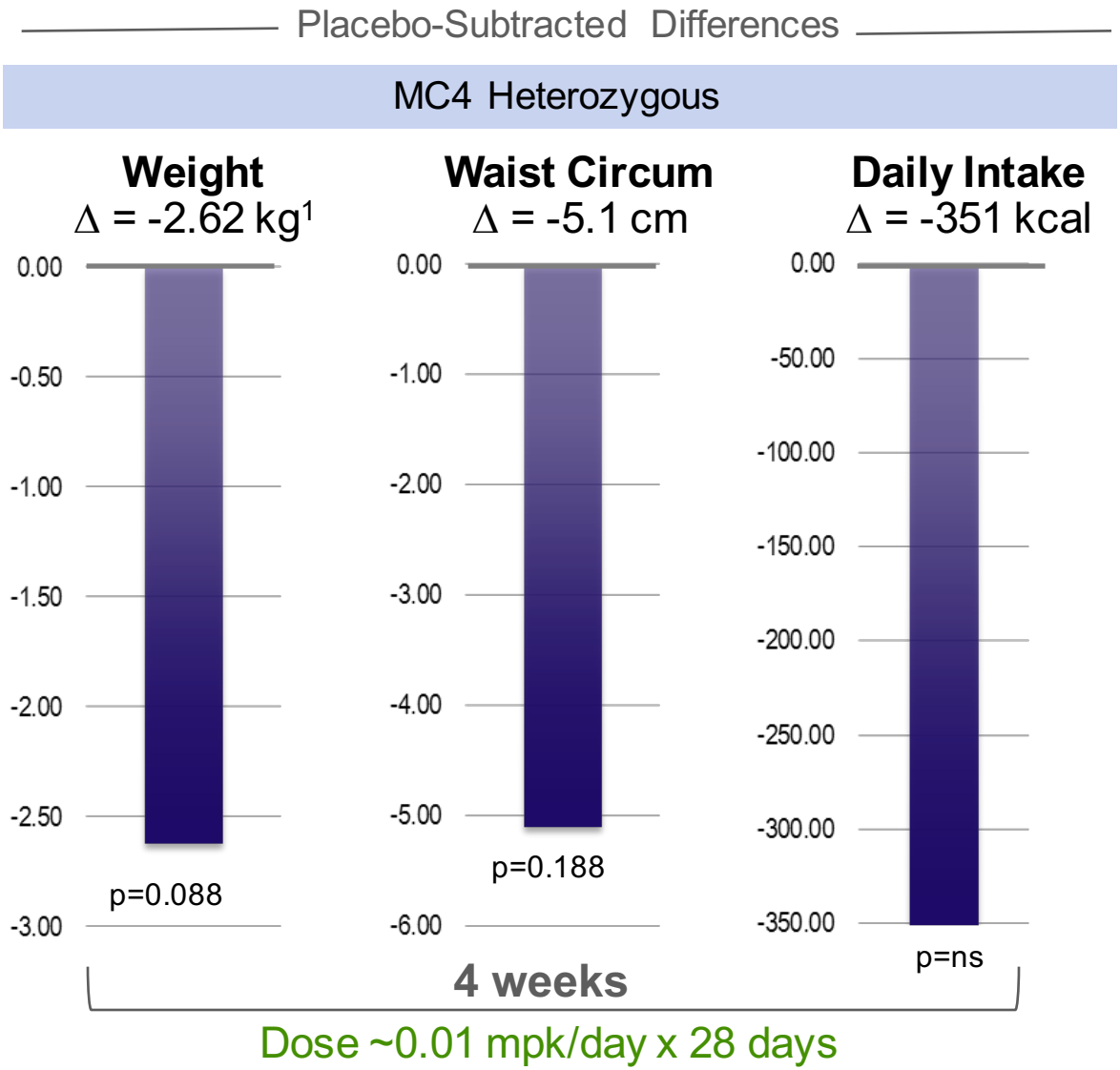
- Pilot, double-blind, placebo (pbo) controlled, randomized, parallel group study
- Eight obese (BMI>30kg/m^2) patients: 6 active/2 pbo
- All with heterozygous MC4R loss of function mutations (see below)
- Treatment: pbo or setmelanotide at 0.01 mg/kg/day (~ 1 mg/day) by continuous subcutaneous infusion x 4 weeks
- Key endpoints: safety, weight loss, waist circumference, and caloric intake

MC4R Heterozygous Variants in the Phase 1b Study

Subject	Variant	Function
601	I269N	Complete Loss of Function
602	G252S	Partial Loss of Function
603	C271Y	Complete Loss of Function
604	Q156X	Complete Loss of Function
605	Q307X	Complete Loss of Function
606	R165Q	Partial Loss of Function
607	G252S	Partial Loss of Function
608	R165W	Partial Loss of Function

Phase 1b trial in MC4R Heterozygous Deficiency Obesity: Results

Initial Proof of Concept in MC4R heterozygous patients



Preliminary data; N=8 (6 active/2 pbo); Circum=circumference; Daily Intake=average difference in caloric intake in over 28d

[1]Setmelanotide group showed weight loss of -3.48 kg, the placebo group showed weight loss of -0.85 kg.

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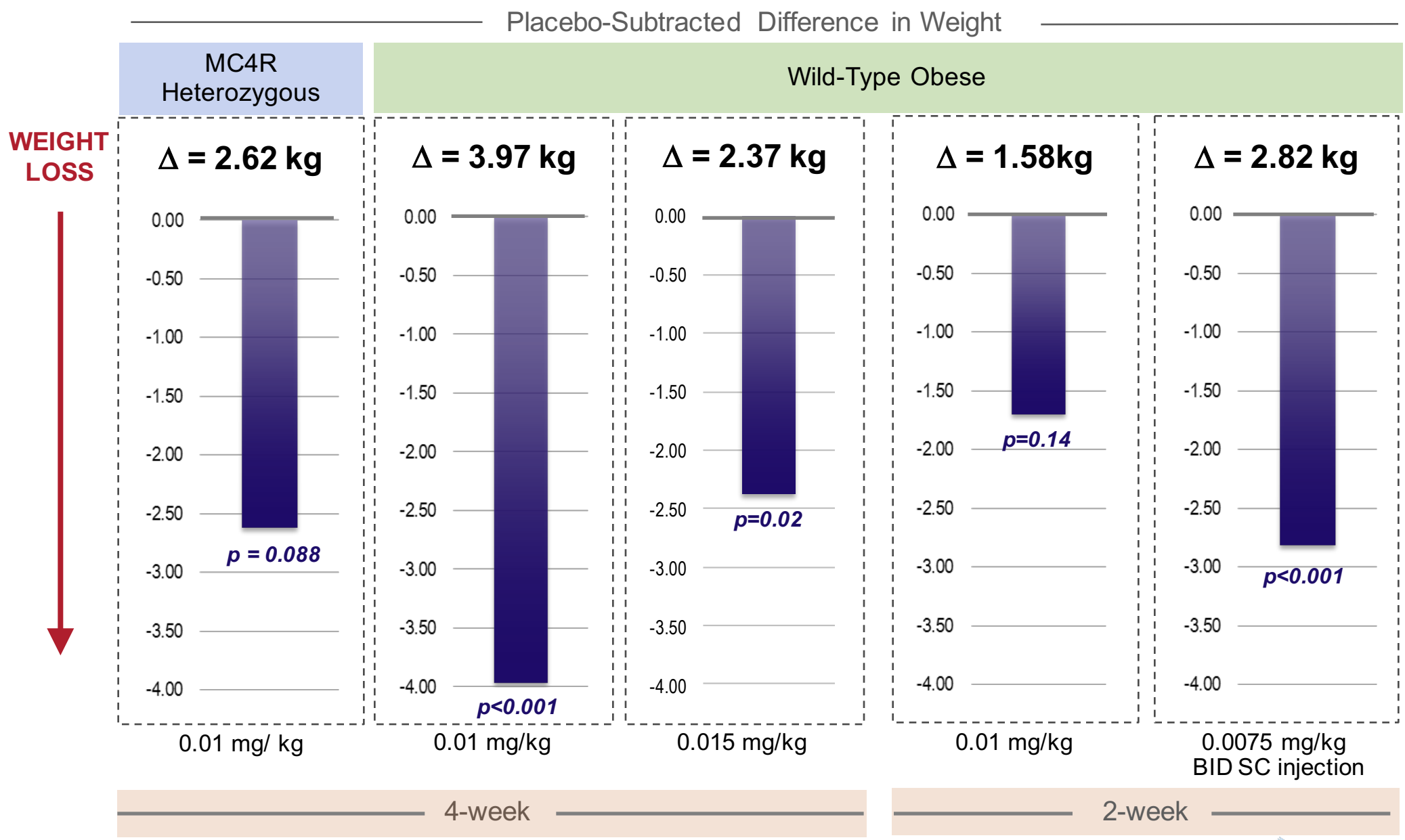
Weight Loss in Four Add'l General Obesity Ph1b cohorts

Weight Loss: ~0.9 kg (0.9%) per Week



N=9 per group (6 active, 3 placebo) except MC4R Heterozygous cohort (6 active, 2 placebo); BID=twice daily

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Phase 1b trial in MC4R Heterozygous Deficiency Obesity: Safety

In this small, 4-week pilot study of patients with MC4R heterozygous deficiency obesity:

- **Setmelanotide was generally well-tolerated, with no SAEs or discontinuations**
- **The most common side effects were headache and skin tanning**
  - The latter due to off-target activity at the related MC1R
- **No clinically important effects on heart rate or blood pressure**

More broadly, setmelanotide has been generally well-tolerated

~200 general obese patients exposed to drug for up to 12 weeks:

- The number and patterns of adverse events (AEs) was generally low, and the intensity of the adverse events was generally mild
- Discontinuations due to AEs were uncommon
- Most AEs were due to mechanism-based effects
  - Little, if any, evidence of blood pressure or heart rate changes[1]
  - Occasional increase in male erections/female arousal
  - Small incidence of nausea and/or vomiting
- Other, non-mechanism based AEs: evenly distributed among active and placebo treatment groups
  - Small incidence of injection site reactions
  - Darkening of skin and skin lesions, such as moles and freckles, in most patients who received setmelanotide
- No clinically relevant changes in electrocardiograms, laboratory data and/or anti-drug antibodies

[1]See Poster T-P-3134: Analysis of the synthetic peptide RM-492 on cardiovascular parameters in three Phase 1b/2a studies

Conclusions

In this 4-week pilot study of patients with MC4R heterozygous deficiency obesity:

- Setmelanotide treatment led to trends in the reduction of weight, waist circumference and caloric intake
- Setmelanotide was generally well-tolerated
- These initial data support initiation of trials in patients with other genetic defects in this important pathway


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