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

Hunger Signals (Ghrelin, NYP)

MC4 Pathway

SATIETY SIGNALS

LEPTIN SIGNAL

POMC Neurons → MSH

Magel2 → PCSK

LepR

MC4R

RM-493

MC4 Neurons

Hunger Signals

SATIETY SIGNAL

LEPTIN SIGNAL

PCSK = PCKS1

↓ Appetite

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

“Upstream” Deficiencies

MC4 pathway

Prader-Willi Syndrome

Leptin Receptor Deficiency

POMC Neurons

POMC Deficiency

POMC Heterozygous Deficiency

Upstream

Downstream

Decreased Appetite

Decreased Weight

POMC deficiency includes both POMC gene deficiency and/or PCSK1 gene deficiency
“Downstream” Deficiency

MC4 Pathway

- Leptin Receptor Deficiency
- POMC Neurons (POMC Deficiency, POMC Heterozygous Deficiency)
- MC4 Neurons

Upstream: Prader-Willi Syndrome
- Magel2
- PCSK

Downstream: MC4R Heterozygous Deficiency
- RM-493
- (setmelanotide)

Decreased Appetite
Decreased Weight
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
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

<table>
<thead>
<tr>
<th>Subject</th>
<th>Variant</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>601</td>
<td>I269N</td>
<td>Complete Loss of Function</td>
</tr>
<tr>
<td>602</td>
<td>G252S</td>
<td>Partial Loss of Function</td>
</tr>
<tr>
<td>603</td>
<td>C271Y</td>
<td>Complete Loss of Function</td>
</tr>
<tr>
<td>604</td>
<td>Q156X</td>
<td>Complete Loss of Function</td>
</tr>
<tr>
<td>605</td>
<td>Q307X</td>
<td>Complete Loss of Function</td>
</tr>
<tr>
<td>606</td>
<td>R165Q</td>
<td>Partial Loss of Function</td>
</tr>
<tr>
<td>607</td>
<td>G252S</td>
<td>Partial Loss of Function</td>
</tr>
<tr>
<td>608</td>
<td>R165W</td>
<td>Partial Loss of Function</td>
</tr>
</tbody>
</table>
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

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

**MC4 Heterozygous**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Δ</th>
<th>Placebo-Subtracted Differences</th>
<th><strong>p</strong>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>-2.62 kg</td>
<td></td>
<td>0.088</td>
</tr>
<tr>
<td>Waist Circum</td>
<td>-5.1 cm</td>
<td></td>
<td>0.188</td>
</tr>
<tr>
<td>Daily Intake</td>
<td>-351 kcal</td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>

Dose ~0.01 mpk/day x 28 days
Weight Loss in Four Add’l General Obesity Ph1b cohorts

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

<table>
<thead>
<tr>
<th>MC4R Heterozygous</th>
<th>Placebo-Subtracted Difference in Weight</th>
<th>Wild-Type Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ = 2.62 kg</td>
<td></td>
<td>Δ = 2.82 kg</td>
</tr>
<tr>
<td>0.01 mg/kg</td>
<td>[Bar chart with p=0.088]</td>
<td></td>
</tr>
<tr>
<td>0.015 mg/kg</td>
<td>[Bar chart with p=0.02]</td>
<td>Δ = 1.58 kg</td>
</tr>
<tr>
<td>0.01 mg/kg</td>
<td>[Bar chart with p=0.14]</td>
<td></td>
</tr>
<tr>
<td>0.0075 mg/kg</td>
<td>[Bar chart with p&lt;0.001]</td>
<td>Δ = 2.37 kg</td>
</tr>
<tr>
<td>2-week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Approximately 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
  - 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

1See 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