Effect of a Melanocortin-4 Receptor Agonist, Setmelanotide, on Obesity and Hyperphagia in Individuals Affected by Alström Syndrome

Joan C. Han,1,2 Fred T. Fiedorek,3 Michelle Hylan,4 Cathy Folster,5 Tarekegn Geberhiwot6 Departments of Pediatrics and Physiology, University of Tennessee Health Science Center, Memphis, TN, USA; Children’s Foundation Research Institute, Le Bonheur Children’s Hospital, Memphis, TN, USA; Rhythm Pharmaceuticals, Boston, MA, USA; Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom

Summary

- This first participant with Alström syndrome to receive setmelanotide experienced a reduction in hunger, weight, body mass index (BMI), percent body fat, and various glycemic and lipid measurements along with an increase in resting energy expenditure (REE).
- Reduction in body weight and hunger scores were consistent with previous clinical studies in participants with POMC or LEPR defects.
- These results support the continued evaluation of setmelanotide for the treatment of obesity and hunger in people with rare genetic disorders of obesity, including Alström syndrome.

Introduction

- Setmelanotide is a melanocortin-4 receptor (MC4R) peptide agonist shown to reduce body weight and hunger scores in individuals affected by rare genetic disorders of obesity resulting from defects in the genes POMC and LEPR.
- Alström syndrome is a rare genetic ciliopathy characterized by early-onset severe obesity, hyperglycemia, retinal dystrophy, sensory hearing loss, cardiomyopathy, and metabolic derangements, including type 2 diabetes mellitus, hypogonadism, and hypothryroidism.
- Preclinical data suggest that setmelanotide can play a role in the central melanocortin pathway (and a component of this pathway, the MC4R pathway), which regulates energy balance and body weight (Figure 1).
- The effect of setmelanotide in participants with Alström syndrome is being investigated in an ongoing phase 2 study (ClinicalTrials.gov identifier: NCT01303543).

Study Design

- To report preliminary data on the effects of setmelanotide on body weight, hunger scores, and safety in an individual diagnosed with Alström syndrome participating in an ongoing phase 2 study of setmelanotide.

Methods

- Study Participants
  - This is a phase 2, intervention, open-label, single-arm study enrolling individuals with rare genetic disorders of obesity, including Alström syndrome.
  - Participants are ≥12 years of age with a BMI ≥30 kg/m² for those ≥18 years of age or ≥95th percentile for age and sex.
  - Participants must have a genetically confirmed diagnosis of rare obesity.
  - Participants with ≥2.0% weight loss from diet intervention or exercise regimens within 2 months of enrollment are excluded.

- Study Design
  - Setmelanotide is administered as a once-daily subcutaneous injection (Figure 2). Initial dose in adolescents is 0.5 mg/day, with dose titration by 0.5 mg increments every 2 weeks (maximum 3 mg).

- Endpoints
  - Primary endpoint is the mean percent change in body weight after 12 weeks at therapeutic dose.
  - Secondary endpoints include safety and tolerability, changes in hunger score, percent body fat, laboratory values, and waist circumference.
  - For participants who continue into the long-term extension study and who consented to participation in a withdrawal phase, secondary endpoints also include reversal of weight loss and hunger reduction.

- Assessments
  - Body weight, body mass index, and heart rate are recorded at each visit.
  - Body composition (as assessed by InBody 770, InBody, South Korea) and skin and physical examinations, plus metabolic, endocrine, hematologic, and pharmacokinetic testing, are also conducted at regular intervals.

- Hunger scores are recorded daily by the participant using the following 3-item hunger questionnaire, with each item scored on a Likert-type scale where 0 equals no hunger at all and 10 equals most hunger.
  - “In the last 24 hours, on average, how hungry did you feel?”
  - “In the last 24 hours, how hungry did you feel when you were the most hungry?”
  - “This morning when you woke up for the day, how hungry did you feel?”

- REE is measured by indirect calorimetry (Parvomedics True One 2400, Parvomedics, Sandy, UT).

- Changes in Metabolic Parameters From Baseline in a 12-Year-Old Male Participant

Table 1. Changes in Metabolic Parameters From Baseline in a 12-Year-Old Male Participant

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline value</th>
<th>Last observation value</th>
<th>Week of last observation</th>
<th>Percent absolute change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average hunger score</td>
<td>4.6</td>
<td>3.0</td>
<td>0</td>
<td>-35.0%</td>
</tr>
<tr>
<td>Morning hunger score</td>
<td>6.1</td>
<td>3.0</td>
<td>0</td>
<td>-50.0%</td>
</tr>
<tr>
<td>Average weight score</td>
<td>53.6</td>
<td>44.4</td>
<td>0</td>
<td>-17.0%</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>190.0</td>
<td>160.0</td>
<td>0</td>
<td>-16.0%</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.8</td>
<td>158.8</td>
<td>0</td>
<td>-5.0%</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.5</td>
<td>26.1</td>
<td>0</td>
<td>-17.0%</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>97.4</td>
<td>91.4</td>
<td>0</td>
<td>-6.0%</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>102.4</td>
<td>89.4</td>
<td>0</td>
<td>-12.0%</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>106.8</td>
<td>99.8</td>
<td>0</td>
<td>-6.5%</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>194.0</td>
<td>101.0</td>
<td>0</td>
<td>-47.0%</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>36.8</td>
<td>34.8</td>
<td>0</td>
<td>-5.9%</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>127.0</td>
<td>78.0</td>
<td>0</td>
<td>-39.0%</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>149.0</td>
<td>98.0</td>
<td>0</td>
<td>-35.0%</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>86.0</td>
<td>65.0</td>
<td>0</td>
<td>-25.0%</td>
</tr>
<tr>
<td>ALT, US units/L</td>
<td>13.0</td>
<td>4.0</td>
<td>0</td>
<td>-69.0%</td>
</tr>
<tr>
<td>ALP, US units/L</td>
<td>1.0</td>
<td>0.4</td>
<td>0</td>
<td>-60.0%</td>
</tr>
<tr>
<td>Na, mmol/L</td>
<td>138.0</td>
<td>142.0</td>
<td>0</td>
<td>3.0%</td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>4.0</td>
<td>3.7</td>
<td>0</td>
<td>-7.0%</td>
</tr>
<tr>
<td>Ca, mmol/L</td>
<td>2.5</td>
<td>2.5</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Creactive, mg/L</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

- Setmelanotide reactivates the MC4R, which regulates energy balance and body weight.
- The dose was reduced to 26 weeks in the study because the participant approached normal body weight (BMI = 18.5th percentile).
- Weight stabilized at 0.5 mg/day.

- Summary
- Hunger scores are recorded daily by the participant using the following 3-item hunger questionnaire, with each item scored on a Likert-type scale where 0 equals no hunger at all and 10 equals most hunger.
- “In the last 24 hours, on average, how hungry did you feel?”
- “In the last 24 hours, how hungry did you feel when you were the most hungry?”
- “This morning when you woke up for the day, how hungry did you feel?”

- Results
- Participants and Baseline Characteristics
  - As of August 2018, 4 participants with Alström syndrome had been enrolled in the study.
  - The first is a 12-year-old white male participant treated for 50 weeks.
  - His baseline weight was 76.6 kg, BMI was 27.8 kg/m² (98th percentile for age and sex); percent body fat was 29.8%; and mean daily hunger scores were 5.5 for most hungry, 4.6 for morning hunger, and 4.1 for average hunger (Figure 3, Table 1).

- Efficacy
  - In the 12-year-old male participant, after 18 weeks (12 weeks on therapeutic dose), his body weight was reduced by 13.3%, and his average hunger, most, and morning hunger scores decreased, dropping from 4.1, 5.5, and 4.6 (of 10) at baseline, respectively, to 3.0, 3.5, and 2.1, respectively.
  - REE increased from 95% predicted (MIF-St. Jeor equation) at baseline to 99% predicted at 18 weeks.
  - At 50 weeks, his body weight, body fat, and hunger scores were reduced.
  - Maximum setmelanotide dosage was 2.0 mg/day.
  - The dose was reduced after 26 weeks in the study because the participant approached normal body weight (BMI = 18.5th percentile).
  - Weight stabilized at 0.5 mg/day.

- Safety
- Setmelanotide was well tolerated.
- Adverse events included increased pigmentation of the skin/nails.
- Average ambulatory 24-hour blood pressure was prehypertensive at baseline and became nonhypertensive after setmelanotide treatment.

- Acknowledgments
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- References