Summary

Updated data from the Bardet-Biedl syndrome (BBS) cohort of the phase 2 proof-of-concept basket study show a reduction in body weight and decreased appetite as shown by lower hunger scores consistent with a previous study of a rare genetic disorder of obesity.

Setmelanotide is generally well tolerated and has a safety profile consistent with previous reports.

These results support the continued evaluation of setmelanotide for treatment of obesity and hunger in individuals with rare genetic disorders of obesity including BBS.

Introduction

Setmelanotide is a melanocortin-4 receptor (MC4R) agonist that reduces body weight and hunger scores in individuals affected by rare genetic disorders of obesity resulting from dysfunction of genes upstream of MC4R.

BBS is a rare disorder characterized by early-onset severe obesity (associated with insatiable hunger [termed hyperphagia]), visual impairment, cognitive difficulties, polycystic renal disease, and hypertension.

BBS genes are implicated in the function of the MC4R pathway, which is a component of the central melanocortin pathway (Figure 1).

The effect of setmelanotide on efficacy and safety measures in individuals with BBS is being investigated in an ongoing phase 2 study (ClinicalTrials.gov identifier: NCT03013543).

Efficacy

Results

Participants and Baseline Characteristics

As of August 2018, 9 individuals with BBS have been enrolled (median duration of study treatment: 31 weeks [range, 18-71 weeks]).

Mean standard error of the mean (SEM) baseline weight among participants was 125.7 ± 3.2 kg. SEM baseline BMI was 44.7 ± 0.5 kg/m².

Baseline characteristics for each participant are listed in Table 1.

Of the 9 participants enrolled by August 2018, 5 had 12 weeks of treatment for assessment of response and 3 withdrew from the study because of lack of weight response.

Table 1. Baseline Characteristics of Participants With BBS Mutations

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age/Sex</th>
<th>Mutation</th>
<th>Baseline weight, kg</th>
<th>Baseline BMI, kg/m²</th>
<th>Hunger score</th>
<th>FPD/SEQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant 1</td>
<td>25M</td>
<td>BBS10</td>
<td>42.8</td>
<td>171.8</td>
<td>51.3</td>
<td>9/2</td>
</tr>
<tr>
<td>Participant 2</td>
<td>61F</td>
<td>BBS2</td>
<td>99.4</td>
<td>122.3</td>
<td>42.8</td>
<td>9</td>
</tr>
<tr>
<td>Participant 3</td>
<td>16F</td>
<td>BBS3</td>
<td>121.6</td>
<td>119.3</td>
<td>49.0</td>
<td>1/2</td>
</tr>
<tr>
<td>Participant 4</td>
<td>17F</td>
<td>BBS12</td>
<td>99.3</td>
<td>81.8</td>
<td>36.9</td>
<td>9</td>
</tr>
<tr>
<td>Participant 5</td>
<td>17F</td>
<td>BBS12</td>
<td>99.3</td>
<td>81.8</td>
<td>36.9</td>
<td>9</td>
</tr>
</tbody>
</table>

Background: BBS, Bardet-Biedl syndrome; BMI, body mass index; F, female; FPD, food problem diary (score range, 0-30); M, male; SEQ, significant event questionnaire (score range, 0-30).

Methods

Participants

This study enrolls individuals with rare genetic disorders of obesity, including BBS.

Participants are ≥12 years of age with a body mass index (BMI) ≥30 kg/m² for those aged ≥12 to <18 years.

Participants must have BBS.

Individuals with ≥2% weight loss from intensive diet or exercise regimens within 2 months of enrollment or ≥1% weight loss that was durably maintained following gastric bypass surgery are excluded.

Study Design

Setmelanotide is administered as a once-daily subcutaneous injection (Figure 2). Initial dosage in adults is 1.0 mg/day, and for adolescents (12 to <18 years of age) is 0.5 mg/day, with dose titration by 0.5 mg increments every 2 weeks (maximum 3.5 mg/day).

Figure 2. Participant 1

Endpoints and Assessments

The primary endpoint is the mean percent change in body weight after 12 weeks at the therapeutic dose.

Secondary endpoints include safety and tolerability and changes in hunger rating, percent body fat, and waist circumference after 3 months of treatment.

Exploratory observer-related questionnaires include the food problem diary (FPD) and the significant event questionnaire (SEQ), which are completed by caregivers of individuals with cognitive impairment.

The FPD is a 10-term observer-reported outcome measure designed to capture common food-related behaviors as recorded daily by caregivers.

- Total scores range from 0-35, with higher scores suggestive of more severe hyperphagia/food-related behaviors.

The SEQ is a 5-term observer-reported outcome measure designed to capture rare food-related behaviors (ie, behaviors expected to occur only with a reduction in hyperphagia in response to treatment) as recorded weekly by caregivers.

- Total scores range from 0-8, with higher scores suggestive of more significant treatment benefit.

Safety

Adverse events included increased pigmentation of the skin/nevi and mild injection site reactions.

No clinically significant detrimental changes in blood pressure or heart rate have been reported.

No serious adverse events were reported.

No discontinuations were due to adverse events.

Objective

To report an update of the effect of setmelanotide on body weight, hunger scores, and safety in 9 individuals diagnosed with BBS in an ongoing phase 2 study.

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