**Summary**

- In the expanded data set from two Phase 3 clinical trials, setmelanotide was associated with weight loss and reductions in hunger in individuals with proopiомelanocortin (POMC) or leptin receptor (LEPR) deficiency and obesity.
- Setmelanotide demonstrated efficacy in POMC deficiency and, although some participants with LEPR deficiency did not lose 20% of baseline weight, substantial effects were observed in approximately half of those with LEPR deficiency.
- No new safety concerns were reported, and setmelanotide was generally well tolerated in individuals with POMC or LEPR deficiency and obesity.

**Key Entry Criteria**

- All participants had biallelic loss-of-function variants in POMC, PCCSY, or LEPR (homozygous or compound heterozygous); adults (aged ≥18 years) had a body mass index ≥30 kg/m²; children or adolescents (aged <18 years) had a weight ≥95th percentile for age.
- Participants were excluded if they had recent diet and/or exercise changes and/or weight loss prior to randomization.
- Children or adolescents with or without a history of obesity from baseline to ~52 weeks on therapeutic dose of setmelanotide.

**Key Endpoints and Assessments**

- **Primary endpoint:** Proportion of patients with ≥10% weight loss at ~52 weeks on setmelanotide.
- **Secondary endpoints:**
  - Mean percent change in body weight at ~52 weeks on setmelanotide.
  - Mean percent change in “most” hunger score at ~52 weeks on setmelanotide and in participants ≥12 years of age.
  - Proportion of participants who achieved ≥25% reduction in the hunger score at ~52 weeks on setmelanotide.
- **Safety and tolerability of setmelanotide** were assessed by reporting treatment-emergent adverse events (AEs) in all participants who received ≥1 dose of setmelanotide.

**Results**

- **Baseline Characteristics**
  - A total of 15 patients with POMC deficiency (10 pivotal cohort, 5 supplemental cohort) and 15 with LEPR deficiency (11 pivotal cohort, 4 supplemental cohort) were enrolled (Table 1).

**Introduction**

- The melanocortin-4 receptor (MC4R) pathway is critical in regulating appetite, body weight, and energy expenditure, and loss-of-function variants in this pathway can cause rare genetic disorders of obesity.
- Impaired signaling of the MC4R pathway by genetic variants in POMC, PCCSY, or LEPR can lead to hyperphagia and early-onset, severe obesity (Figure 1).

**Methods**

- In the primary analyses of two pivotal Phase 3 trials, the MC4R agonist setmelanotide was associated with significant reductions in body weight and hunger in 21 patients with obesity due to POMC or LEPR deficiency.

**Objective**

- To determine the effect of the MC4R agonist setmelanotide on body weight, hunger, and safety outcomes in an expanded cohort of patients with POMC/proopiomelanocortin convertase subtilisin/kexin type 1 or LEPR deficiency and obesity from the pivotal Phase 3 clinical trials.

**Study Design**

- In 2 single-arm, multicenter, Phase 3 trials of setmelanotide in patients with obesity due to POMC (NCT012895192) or LEPR deficiency (NCT010287950), patients aged ≥6 years received setmelanotide at the individualized therapeutic dose for 12 weeks.

- The first–10 participants with POMC or LEPR deficiency were enrolled in each trial (pivotal cohort).
- Because of the rarity of these genetic diseases, enrollment was kept open after pivotal participants were enrolled to collect additional supporting data from a supplementary cohort.

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>POMC deficiency</th>
<th>LEPR deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>17 (1.30)</td>
<td>17 (1.08)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>40.2 (5.8)</td>
<td>40.2 (5.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>8 (69.6)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latin American</td>
<td>2 (13.3)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>White or European</td>
<td>11 (73.3)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Weight, mean (SD) kg</td>
<td>111.3 (8.4)</td>
<td>113.9 (12.8)</td>
</tr>
<tr>
<td>Most hunger score, mean (SD)</td>
<td>8.1 (0.8)</td>
<td>9.1 (1.1)</td>
</tr>
</tbody>
</table>

**Efficacy**

- A total of 85.7% of patients in the POMC trial (12/14; P = 0.0001) and 53.3% of patients in the LEPR trial (8/15; P = 0.0001) achieved ≥10% weight loss at ≥60 days.

- The mean (standard deviation) [SD] percent change in body weight from baseline to ~52 weeks was −25.8% (7.8%; P = 0.0001) and −12.3% (7.5%; P < 0.0001) in the POMC and LEPR trials, respectively (Figure 3).

**Safety Outcomes**

- The most common AEs were injection site reaction and hypoglycemia (Table 2).

- There were no treatment-related serious AEs.

**Figure 4. Average percent change in daily hunger score in participants with (A) POMC and (B) LEPR deficiency obesity from baseline to ~52 weeks on therapeutic dose of setmelanotide.**

- In patients aged ≥12 years, the mean (SD) percent change in hunger score at 52 weeks was −27.1% (−28.1%) and −42.7% (−27.5%) in the POMC and LEPR trials, respectively (Figure 4).

**Table 2. Treatment-Emergent AEs in Participants Receiving Setmelanotide**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>POMC deficiency</th>
<th>LEPR deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11 (73.3)</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>13 (86.7)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>11 (73.3)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (53.3)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (53.3)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (33.3)</td>
<td>2 (13.3)</td>
</tr>
</tbody>
</table>

**References**