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

P1-P105

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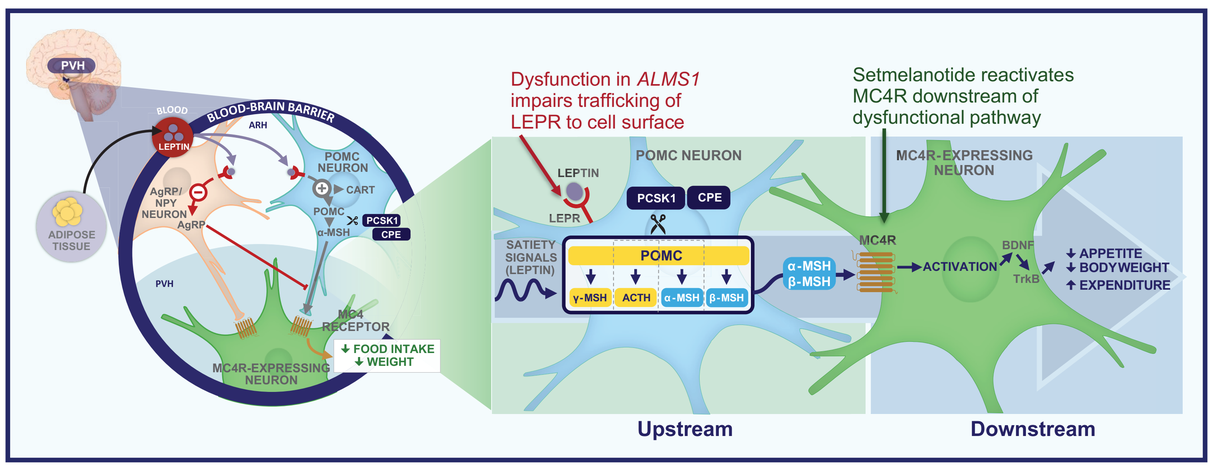
Summary

- **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[1,2]**
  - **The safety profile of setmelanotide was consistent with previous reports, and to date, adverse events have been mild, transient, and generally well tolerated[1,3]**
- **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*[1,4]
- Alström syndrome is a rare genetic ciliopathy characterized by early-onset severe obesity, hyperphagia, retinal dystrophy, sensory hearing loss, cardiomyopathy, and metabolic derangements, including type 2 diabetes mellitus, hypogonadism, and hypothyroidism[5,6]
  - Preclinical data suggest that cilia 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)[4,7,8]
- The effect of setmelanotide in participants with Alström syndrome is being investigated in an ongoing phase 2 study (ClinicalTrials.gov identifier: NCT03013543)

Figure 1. The MC4R pathway, a component of the central melanocortin pathway, regulates appetite and energy balance, and mutations in this pathway can result in rare genetic disorders of obesity.[8-10]



[a]AgRP, agouti-related protein; ALMS1, Alström syndrome protein 1; ARH, arcuate nucleus; BDNF, brain-derived neurotrophic factor; CART, cocaine- and amphetamine-related transcript; CPE, carboxypeptidase E; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PVH, paraventricular nucleus of hypothalamus; TrkB, neurotrophin receptor.

Objective

- 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

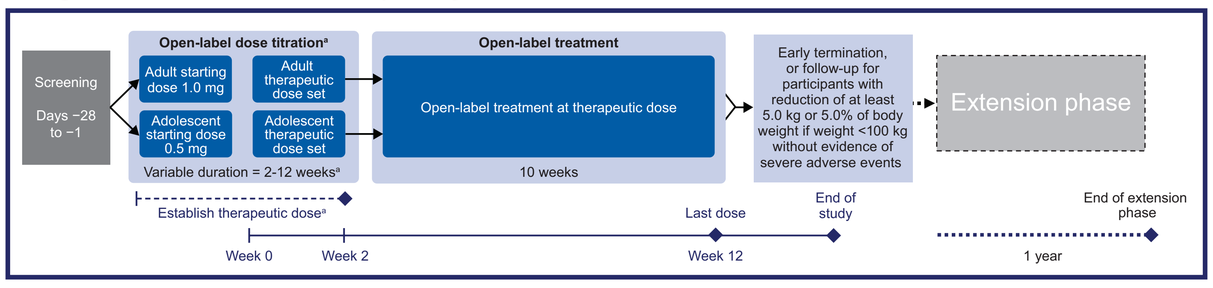
Study Participants

- This is a phase 2, interventional, 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 weight >97th percentile for age/sex on a growth chart for those ≥12 to <18 years of age
  - Participants must have a genetically confirmed diagnosis of a rare disorder of obesity
- Participants with >2.0% weight loss from intensive diet or exercise regimens within 2 months of enrollment or >10.0% 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 adolescents is 0.5 mg/day, with dose titration by 0.5-mg increments every 2 weeks (maximum 3.0 mg)

Figure 2. Phase 2 basket study design and treatment duration.



[a]The last 2 weeks of the open-label dose titration phase in which the optimal therapeutic dose for a participant is established is considered the first 2 weeks of the open-label treatment phase. Participants then receive an additional 10 weeks of active treatment in the open-label treatment phase for a total of 12 weeks of treatment at the therapeutic dose.

Endpoints

- The 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, blood pressure, 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)

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 78.6 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 13.0%, and his average hunger, most hungry, and morning hunger scores improved, dropping from 4.1, 5.5, and 4.6 (of 10.0) at baseline, respectively, to 3.0, 3.0, and 2.1, respectively
- REE increased from 95% predicted (Mifflin-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 <85th percentile)
  - Weight stabilized at 0.5 mg/day

Figure 3. Setmelanotide reduced weight and hunger score throughout 50 weeks of treatment in a 12-year-old male participant.

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

Measure	Baseline value	Last observation value	Week of last observation	Percent or absolute change
Most hungry score	5.5	3.0	50	−45.0%
Morning hunger score	4.6	3.0	50	−35.0%
Average hunger score	4.1	3.0	50	−27.0%
Weight, kg	78.6	59.4	50	−24.0%
Height, cm	168.1	168.8	50	0.0%
BMI, kg/m²	27.8	20.8	50	−25.0%
BMI percentile	97.8	75.3	50	−23.0%
Waist circumference, cm	102.4	81.4	50	−21.0%
BIA	29.8	18.2	50	−39.0%
ALT, U/L	120.0	93.0	50	−27.0
HbA1c, mmol/mol	5.6	5.2	45	−0.4
Triglycerides, mg/dL	164.0	101.0	45	−38.0%
HDL, mg/dL	44.0	58.0	45	32.0%
LDL, mg/dL	127.0	78.0	45	−39.0%
Hip circumference, cm	104.6	92.6	45	−12.0
Neck circumference, cm	36.0	33.8	45	−2.2
SBP, mm Hg	124.0	98.0	50	−26.0
DBP, mm Hg	86.0	69.0	50	−17.0

ALT, alanine aminotransferase; BIA, bioelectrical impedance analysis; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Safety

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

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