Efficacy and Safety of the MC4R Agonist Setmelanotide in LEPR Deficiency Obesity: A Phase 3 Trial

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Summary

- **Individuals with leptin receptor (LEPR) deficiency obesity who received setmelanotide experienced clinically meaningful weight loss and reduction in hunger scores**
- **Setmelanotide was generally well tolerated, and no serious safety concerns were identified**
- **Overall, the efficacy and safety profile of setmelanotide supports its potential use as a novel treatment for early-onset severe obesity and hyperphagia caused by LEPR deficiency**

Introduction

- Rare genetic variants in leptin receptor (*LEPR*) disrupt leptin-melanocortin signaling, thereby reducing melanocortin 4 receptor (MC4R) activation, resulting in early-onset severe obesity and insatiable hunger (termed hyperphagia)[1,2]
- Setmelanotide is an MC4R agonist that was previously shown to reduce body weight and hunger scores in individuals affected by rare genetic disorders of obesity resulting from dysfunction of genes upstream of MC4R, including 3 individuals with LEPR deficiency[3,4]
  - Currently, setmelanotide is being investigated in participants with other rare genetic disorders of obesity, including proopiomelanocortin deficiency, Bardet-Biedl syndrome, and Alström syndrome

Objectives

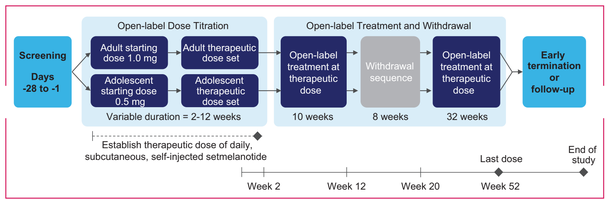
- To determine the effect of the MC4R agonist setmelanotide on body weight, hunger, and safety outcomes in individuals ≥6 years of age with obesity caused by confirmed LEPR deficiency obesity

Methods

Study Design

- This open-label, multicenter, placebo-controlled, phase 3 clinical trial (ClinicalTrials.gov identifier: NCT03287960) assessed the efficacy and safety of daily self-injected setmelanotide in participants with LEPR deficiency obesity (Figure 1)

Figure 1. Study design.



Participants who reached a threshold body weight loss of 5 kg (or 5% if <100 kg) in the open-label active treatment phase entered an 8-week placebo-controlled withdrawal phase and then resumed setmelanotide at the therapeutic dose for an additional 32 weeks. Participants who did not achieve the weight loss threshold were not included in the placebo period.

- Once participants received their therapeutic dose for 2 weeks, they entered a 10-week, open-label active treatment phase
- Participants were instructed to not change their regular diet or exercise regimen

Key Entry Criteria

- All participants were biallelic for loss-of-function *LEPR* variants (homozygote or compound heterozygote); adults (aged ≥18 years) had a body mass index (BMI) of ≥30 kg/m^2; children or adolescents (aged ≥6 years to <18 years) had a weight of >97th percentile for age
- Participants were excluded if they had recent diet and/or exercise regimens resulting in weight loss or stabilization or had prior gastric bypass surgery resulting in >10% weight loss with no evidence of weight regain

Endpoints and Assessments

- The primary endpoint was the proportion of all participants who achieved ≥10% body weight loss compared with baseline at ~1 year on therapeutic dose
- The first key secondary endpoint was mean percentage change in body weight at ~1 year on therapeutic dose, and the second key secondary endpoint was mean percentage change in "most hunger score" at ~1 year on therapeutic dose; these endpoints were analyzed in participants who met the body weight loss threshold
- The third key secondary endpoint was the proportion of all participants who achieved a ≥25% reduction in "most hunger" score at ~1 year on therapeutic dose
- "Most hunger" score was determined on a 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"
- Other secondary endpoints included metabolic parameters and body composition
- The safety and tolerability of setmelanotide were assessed by vital signs (including heart rate and blood pressure), as well as the frequency and severity of adverse events in all participants who received ≥1 dose of setmelanotide
- A post hoc analysis of BMI Z-scores in participants aged <19 years was conducted

Results

Participant Disposition and Baseline Characteristics

- 11 participants aged 12 to 37 years with LEPR deficiency obesity were enrolled with a baseline mean BMI of 48.2 kg/m^2 and baseline "most hunger" score of 7.1 (Table 1)

Table 1. Baseline Participant Characteristics

Parameter	
Age, mean (SD) [range], y	23.4 (8.7) [12-37]
Male, n (%)	3 (27)
Genotype, n (%)	
Compound heterozygous	6 (55)
Homozygous	5 (45)
Ethnicity, n (%)	
White	10 (91)
Other (South Asian)	1 (9)
Weight, mean (SD) [range], kg	133.3 (26.0) [89.4-170.4]
BMI, mean (SD) [range], kg/m^2	48.2 (10.5) [35.8-64.6]
Most hunger score, mean (SD) [range][a]	7.1 (1.0) [5-8]

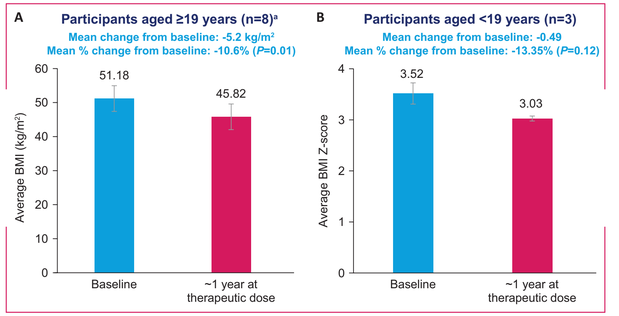
BMI, body mass index; SD, standard deviation. [a]Most hunger score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"

- 9 participants completed the trial; 2 participants discontinued the study early (n=1 possibly treatment-related mild hypereosinophilia and n=1 death from road traffic accident)

Efficacy

- 5 out of 11 participants (45%) achieved at least 10% weight loss from baseline to ~1 year on therapeutic dose (*P*=0.0001)
- The mean percent change from baseline in body weight at ~1 year on therapeutic dose was -12.5% (n=7; *P*<0.0001)
- During the placebo withdrawal period, participants (n=7) gained an average of 4.97 kg
- From baseline to ~1 year on therapeutic dose, participants aged ≥19 years had an average change in BMI of -5.2 kg/m^2, and participants aged <19 years had an average change in BMI Z-score of -0.49 (Figure 2)

Figure 2. Mean change in **(A)** BMI in participants aged ≥19 years and **(B)** BMI Z-score in participants aged <19 years from baseline to ~1 year on therapeutic dose.



BMI, body mass index. [a]One participant was not included in the ~1-year measurement because of discontinuation due to treatment-related adverse event. Population includes imputed data based on linear mixed effect model from n=1 participant who died from a car accident after 26 weeks at therapeutic dose. Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of n. BMI Z-score was based on World Health Organization standards.

- There was a significant reduction in mean percent change in "most hunger" score from baseline to ~1 year on therapeutic dose (-43.7%; n=7; *P*<0.0001)
- During the placebo withdrawal period, participants' mean "most hunger" score increased to 6.4 (n=6) from 3.1 (n=7) during the first open-label active treatment phase
- 8 out of 11 participants (73%) had ≥25% reduction in "most hunger" scores from baseline to ~1 year on therapeutic dose (*P*<0.0001)

Metabolic Parameters and Body Composition

- Setmelanotide was associated with significant changes in cholesterol levels but was not associated with significant changes in glucose or HbA_{1c} levels (Table 2)

Table 2. Changes in Metabolic Parameters From Baseline to ~1 Year at Therapeutic Dose

Mean parameter	Baseline (N=11)	~1 year at therapeutic dose (n=9)	Percent change from baseline (n=9) *P* value
Glucose and HbA_{1c}			
Fasting glucose, mg/dL (SD)	106.1 (49.2)	108.9 (55.4)	-0.7 (7.0); *P*=0.78
HbA_{1c}, % (SD)	5.7 (0.8)[a]	5.5 (0.7)[b]	-4.9 (7.8)[c]; *P*=0.23
Lipids			
HDL cholesterol, mg/dL (SD)	41.9 (14.4)	49.2 (16.2)	19.6 (24.0); *P*=0.04
LDL cholesterol, mg/dL (SD)	105.9 (24.8)	93.3 (22.1)	-10.0 (12.1); *P*=0.04
Triglycerides, mg/dL (SD)	112.3 (46.0)	96.5 (30.2)	-7.0 (26.6); *P*=0.46

HbA_{1c}, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation. [a]n=7. [b]n=5.

- Setmelanotide was associated with significant reductions in lean mass and fat mass (Table 3)

Table 3. Changes in Body Composition From Baseline to ~1 Year at Therapeutic Dose

Parameter	Percent change from baseline (n=8[a]) *P* value
Total body mass, mean (SD)[b]	-4.9 (14.7); *P*=0.41
Lean muscle mass, mean (SD)	-9.4 (5.8); *P*=0.003
Total fat mass, mean (SD)	-12.4 (14.5); *P*=0.05

SD, standard deviation. [a]Unless otherwise noted. [b]n=7; sensitivity analysis based on data entry error.

Safety

- The most commonly reported treatment-related adverse events (AEs) included injection-site reactions, skin and subcutaneous tissue disorders (eg, pigmentation disorder, skin hyperpigmentation, discoloration), and nausea (Table 4)

Table 4. Treatment-Emergent Adverse Events in Participants Receiving Setmelanotide

Parameter	n (%)
Treatment-related AEs	11 (100)
Injection-site reaction	11 (100)
Skin and subcutaneous tissue disorders[a]	8 (73)
Nausea	4 (36)
Serious AEs	3 (27)
Serious treatment-related AEs	0
Treatment-related AEs leading to discontinuation	1 (9)
Treatment-emergent AEs leading to death[b]	1 (9)

AE, adverse event; n, participants. [a]Including pigmentation disorder, skin hyperpigmentation, and discoloration. [b]Participant died from injuries sustained during a car accident; this event was not considered related to setmelanotide treatment.

- 4 serious AEs (n=3 participants) were reported; none were considered related to setmelanotide treatment
  - These events were cholecystitis, suicidal ideation, gastric banding reversal, and a road traffic accident leading to the death of 1 participant
- 1 participant discontinued the trial because of mild hypereosinophilia possibly related to setmelanotide treatment
- There were no reported cardiovascular AEs related to setmelanotide
- Setmelanotide was not associated with significant changes in blood pressure or heart rate
  - The mean percent change in diastolic and systolic blood pressure (mm Hg) was -1.6% (*P*=0.73) and -3.8% (*P*=0.29), respectively (n=9)
  - The mean percent change in heart rate (beats/minute) was -1.3% (n=9; *P*=0.80)

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