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

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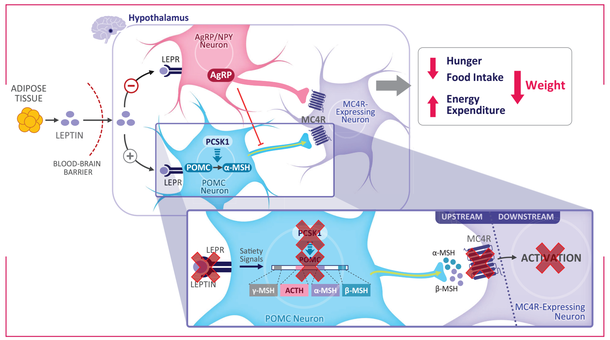
Summary

- In this phase 3 trial, setmelanotide was associated with clinically meaningful weight loss and reduction in hunger scores in individuals with proopiomelanocortin (POMC) or proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency obesity
- No new safety concerns emerged, and setmelanotide was generally well tolerated in individuals with POMC or PCSK1 deficiency obesity
- Further evaluation of setmelanotide is warranted in other disorders resulting from variants in the central melanocortin pathway that cause impaired melanocortin 4 receptor (MC4R) activation

Introduction

- Rare genetic variants in *POMC* and *PCSK1* impair signaling in the central melanocortin pathway, reducing MC4R activation, which results in early-onset severe obesity and insatiable hunger (termed hyperphagia; Figure 1)[1,2]

Figure 1. The MC4R pathway, a component of the central melanocortin 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.[1-3,6]



ACTH, adrenocorticotropic hormone; AgRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

- Setmelanotide is an MC4R agonist that was previously shown to reduce body weight and hunger scores in individuals with variants in genes whose products are upstream of MC4R, including 2 individuals with POMC deficiency obesity[6,7]
  - Currently, setmelanotide is being investigated in individuals with other rare genetic disorders of obesity, including leptin receptor deficiency, Bardet-Biedl syndrome, and Alström syndrome

Objective

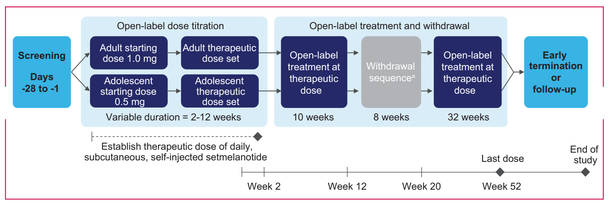
- To determine the effect of the MC4R agonist setmelanotide on body weight, hunger, and safety outcomes in individuals aged ≥6 years with confirmed POMC or PCSK1 deficiency obesity

Methods

Study Design

- This open-label, multicenter, placebo-controlled, phase 3 clinical trial (ClinicalTrials.gov identifier: NCT02896192) assessed the efficacy and safety of setmelanotide in participants with POMC or PCSK1 deficiency obesity (Figure 2)
- Once participants received their therapeutic dose of setmelanotide for 2 weeks, they entered a 10-week, open-label active treatment phase
- 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 were instructed to not change their regular diet or exercise regimen

Figure 2. Study design.



[a]Of the 9 participants who entered the placebo withdrawal period, 8 received treatment during the first 4 weeks and then placebo during the subsequent 4 weeks; 1 received placebo during the first 4 weeks and then was initiated back on treatment for the second 4 weeks.

Key Entry Criteria

- All participants were biallelic for loss-of-function variants in *POMC* or *PCSK1* (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 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
- Secondary endpoints were
  - Mean percent change in body weight from baseline to ~1 year on therapeutic dose, which was analyzed in participants who achieved the weight loss threshold by the end of the first open-label period
  - Mean percent change in "most hunger" score from baseline to ~1 year on therapeutic dose, which was analyzed in participants aged ≥12 years who achieved the weight loss threshold by the end of the first open-label active treatment phase
    - "Most hunger" score was determined on an 11-point Likert scale, where 0 = not hungry at all and 10 = hungriest possible, using the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"
  - The proportion of participants who achieved a ≥25% reduction in "most hunger" score at ~1 year on therapeutic dose, which was analyzed in participants aged ≥12 years who received ≥1 dose of setmelanotide
  - 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 (AEs) in all participants who received ≥1 dose of setmelanotide
- BMI Z-scores in participants aged <19 years were analyzed in a post hoc analysis

Results

Participant Population and Baseline Characteristics

- This trial enrolled 10 participants aged 11 to 30 years with confirmed POMC deficiency obesity (n=9; age range, 11-30 years) or PCSK1 deficiency obesity (n=1; aged 11 years; Table 1)
  - 2 participants were aged <12 years
- 9 participants (90%) completed the trial; 1 participant with POMC deficiency obesity withdrew during the first open-label treatment phase because they did not meet the weight loss threshold

Table 1. Baseline Participant Characteristics

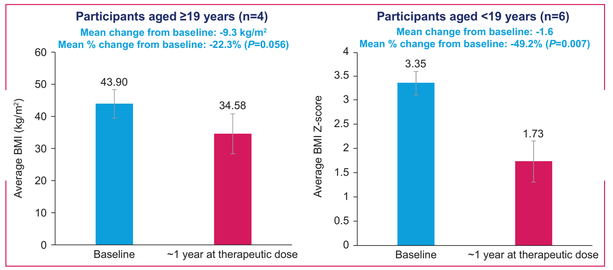
Parameter	
Genotype, n (%)	
POMC	9 (90)
PCSK1	1 (10)
Age, mean (SD) [range], y	18.4 (6.2) [11-30]
Male, n (%)	5 (50)
Ethnicity, n (%)	
Hispanic or Latino	1 (10)
Not Hispanic or Latino	8 (80)
Unknown	1 (10)
Weight, mean (SD) [range], kg	118.7 (37.5) [55.9-186.7]
BMI, mean (SD) [range], kg/m^2	40.4 (9.1) [26.6-53.3]
Most hunger score, mean (SD) [range][a]	8.0 (0.75) [7-9]

BMI, body mass index; SD, standard deviation. [a]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?"

Efficacy

- 8 of 10 participants (80%) achieved ≥10% weight loss from baseline to ~1 year on therapeutic dose (*P*<0.0001)
  - The participant with PCSK1 deficiency obesity who did not meet the primary endpoint had confounding comorbidities and received treatment with risperidone for ~20 weeks, which made responses difficult to assess
  - The second participant who did not meet the primary endpoint was later determined to possibly not have had a loss-of-function variant in *POMC*
- Mean percent change in body weight from baseline to ~1 year on therapeutic dose was -25.4% (n=9; *P*<0.0001)
- From baseline to ~1 year on therapeutic dose, participants aged ≥19 years had an average change in BMI of -9.3 kg/m^2, and participants aged <19 years had an average reduction in BMI Z-score of -1.6 (Figure 3)

Figure 3. Mean change in BMI in participants aged ≥19 years and BMI Z-score in participants aged <19 years from baseline to ~1 year on therapeutic dose.



BMI, body mass index. 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 (-27.1%; n=7; *P*=0.0005)
- 4 of 8 participants (50%) achieved ≥25% reduction in "most hunger" scores at ~1 year on therapeutic dose (*P*=0.0004)
- During the placebo withdrawal period, participants gained an average of 5.52 kg (n=8), and participants' mean "most hunger" score (n=6) increased from 4.87 during the first open-label active treatment phase to 7.10

Metabolic Parameters and Body Composition

- Setmelanotide was associated with changes in levels of fasting glucose and lipids from baseline to ~1 year at therapeutic dose (Table 2)
- Mean percent changes in total body mass, lean muscle, and total fat mass were -23.6% (*P*=0.0003), -10.3% (*P*=0.015), and -36.9% (*P*=0.0002), respectively

Table 2. Changes in Metabolic Parameters From Baseline to ~1 Year at Therapeutic Dose (N=10)

	Baseline	~1 year at therapeutic dose	Percent change from baseline
Glucose and HbA_{1c}			
Fasting glucose, mean (SD), mg/dL	135.8 (107.7)	107.0 (85.5)	-17.2 (18.8); *P*=0.02
HbA_{1c}, mean (SD), %	6.1 (1.8)	5.8 (1.9)	-4.0 (10.5); *P*=0.26
Lipids			
HDL cholesterol, mean (SD), mg/dL	40.4 (17.7)	52.9 (14.1)	45.0 (43.8); *P*=0.01
LDL cholesterol, mean (SD), mg/dL	88.7 (25.9)	80.6 (28.2)	-7.7 (23.1); *P*=0.32
Triglycerides, mean (SD), mg/dL	178.4 (158.3)	78.9 (24.9)	-36.6 (30.4); *P*=0.004

HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Safety

- The most commonly reported treatment-related AEs included injection-site reactions, hyperpigmentation, and nausea/vomiting (Table 3)

Table 3. Treatment-Emergent AEs in Participants Receiving Setmelanotide

Parameter	n (%)
Treatment-related AEs	10 (100)
Injection-site reaction	10 (100)
Hyperpigmentation	10 (100)
Nausea	5 (50)
Vomiting	3 (30)
Serious AEs	4 (40)
Serious treatment-related AEs	0
Treatment-emergent AEs leading to discontinuation	0
Treatment-emergent AEs leading to death	0

AE, adverse event.

- 5 serious AEs were reported in 4 participants; none were considered related to setmelanotide treatment
  - These events were depression, major depression, acute adrenocortical insufficiency, pneumonia, and pleurisy
- There were no reported cardiovascular AEs related to setmelanotide
- Setmelanotide was not associated with changes in blood pressure or heart rate (N=10)
  - The mean percent change in diastolic and systolic blood pressure (mm Hg) was -1.8% (*P*=0.38) and -1.4% (*P*=0.42), respectively
  - The mean percent change in heart rate (beats/minute) was -5.8% (*P*=0.14)

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