Long-term Weight and Hunger Reduction With Setmelanotide in Individuals With POMC Deficiency Obesity

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266

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Summary

- **In this long-term extension (LTE) trial, setmelanotide demonstrated durable weight and hunger reduction beyond 52 weeks in individuals with proopiomelanocortin (POMC) and proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency obesity**
- **No new safety concerns emerged, providing a rationale for long-term use of setmelanotide in this population**
- **Further evaluation of setmelanotide for long-term use is warranted in other disorders resulting from variants that cause impaired melanocortin-4 receptor (MC4R) activation**

Introduction

- The central melanocortin pathway, which includes the MC4R pathway, plays a pivotal role in the regulation of body weight[1]
- Rare genetic variants in POMC/PCSK1, components of the MC4R pathway, result in impaired MC4R activation leading to early-onset severe obesity and hyperphagia[1,2]
- In phase 2 and 3 trials, treatment with the MC4R agonist setmelanotide led to weight and hunger reduction in participants with POMC/PCSK1 deficiency obesity[3,4]
  - Setmelanotide is also 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 long-term durability and safety of the MC4R agonist setmelanotide in individuals with POMC/PCSK1 deficiency obesity

Methods

Study Design

- This open-label active treatment LTE trial (NCT03651765) assessed the safety and tolerability of setmelanotide in participants who had completed an index trial on treatment of setmelanotide. Efficacy was assessed as an exploratory endpoint
- Participants continued setmelanotide at the individual dose determined in the index trial
- Participants were evaluated every 3 months for adverse events and key exploratory endpoint metrics

Key Inclusion Criteria

- Eligible participants were individuals (aged ≥6 years) who had completed an index trial of setmelanotide and demonstrated an adequate safety profile and meaningful clinical benefit
  - Here, data from participants with POMC/PCSK1 deficiency obesity are reported

Endpoints and Assessments

- Key primary endpoints were to characterize the safety and tolerability of setmelanotide, as assessed by the frequency and severity of adverse events
- Key exploratory endpoints included long-term assessment of continued or maintained weight loss and hunger
  - "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?"

Results

Participant Disposition and Baseline Characteristics

- Nine participants (POMC, n=8; PCSK1, n=1) from a related phase 3 trial (NCT02896192)[4] entered the LTE (Table 1)
  - As of this interim analysis (April 16, 2020), 5 participants have completed 89 weeks of treatment in the LTE; 3 participants are ongoing
- Index trial baseline and LTE baseline mean (standard deviation) weights were 115.0 (37.8) and 83.6 (22.1) kg, respectively

Table 1. Baseline Participant Characteristics

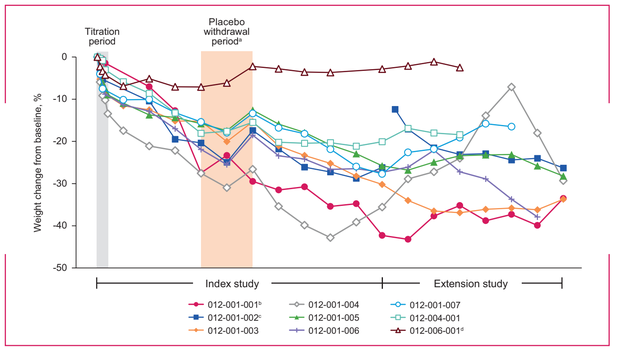
	Participants (N=9)
Age at index study enrollment, mean (SD) [range], y	16.6 (4.8) [11–25]
Sex, n (%)	
Male	5 (55.6)
Female	4 (44.4)
Race, n (%)	
White	7 (77.8)
Other	2 (22.2)
Ethnicity, n (%)	
Hispanic or Latino	1 (11.1)
Not Hispanic or Latino	8 (88.9)
Weight, mean (SD) [range], kg	
Index	115.0 (37.8) [55.9–186.7]
LTE	83.6 (22.1) [54.3–121.9]
BMI, mean (SD) [range], kg/m^2	
Index	39.0 (8.3) [26.6–49.9]
LTE	28.1 (7.1) [21.3–45.0]

BMI, body mass index; LTE, long-term extension; SD, standard deviation.

Efficacy Outcomes

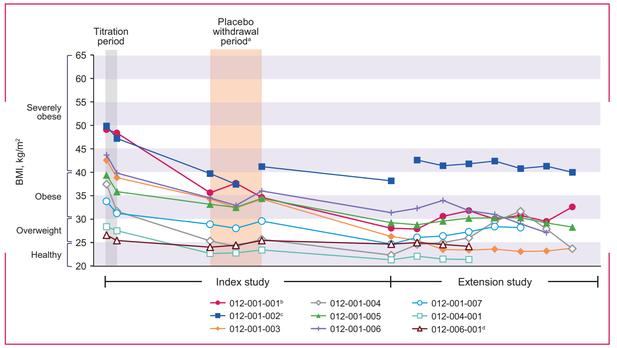
- The mean (standard deviation) percent change in body weight from index baseline through week 89 was −30.2% (3.3%; n=5), with minimal change occurring from LTE baseline through week 89 (mean [standard deviation] percent change: 0.1% [12.4%]; n=5) (Figure 1)
  - Similarly, the mean (standard deviation) absolute change in body weight from index baseline through week 89 was −40.2 (12.6) kg (n=5), with minimal change occurring from LTE baseline through week 89 (mean [standard deviation] change: −0.5 [13.4] kg; n=5)
- The mean (standard deviation) percent change in body mass index from index baseline was −32.5% (9.1%; n=5), with minimal change occurring from LTE baseline through week 89 (mean [standard deviation] percent change: −0.4% [11.1%]; n=5) (Figure 2)
  - 55.6% of participants (5/9) had numerically reduced body mass index from LTE baseline at the most recent follow-up

Figure 1. Percent change in weight from baseline.



[a]8-week placebo withdrawal period consisted of 4 weeks of active drug and then 4 weeks of placebo. Unscheduled visits not included. [b]Patient received placebo then active drug during placebo withdrawal period. [c]Patient off drug between index and extension study. [d]Patient on risperidone index study weeks 16–32.

Figure 2. Body mass index by study week.



BMI, body mass index. [a]8-week placebo withdrawal period consisted of 4 weeks of active drug and then 4 weeks of placebo. Unscheduled visits not included. [b]Patient received placebo then active drug during placebo withdrawal period. [c]Patient off drug between index and extension study. [d]Patient on risperidone index study weeks 16–32.

- The mean (standard deviation) percent change in most hunger score from index baseline through week 89 was −8.2% (27.8%; n=5), with minimal change occurring from LTE baseline through week 89 (mean [standard deviation] percent change: 10.0% [46.9%]; n=5)
  - Similarly, the mean change from baseline most hunger score was stable through week 89 (Table 2)

Table 2. Most Hunger Score[a]

	Index study, mean (SD)	Extension study, mean (SD)
Baseline score	8.0 (0.8)	6.4 (2.6)
Change from baseline		
LTE week 13	−1.1 (2.6)	0.4 (3.1)
LTE week 25	−1.3 (2.8)	0.3 (3.2)
LTE week 37	−1.7 (2.4)	−0.1 (3.3)
LTE week 53	−1.3 (2.6)	0.3 (2.6)
LTE week 65	−0.7 (2.0)	0.9 (3.1)
LTE week 77	−0.8 (2.3)	−0.2 (3.4)
LTE week 89	−0.8 (2.3)	0.0 (3.2)

LTE, long-term extension; SD, standard deviation. [a]"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?"

Safety Outcomes

- Common adverse events (Table 3) were upper respiratory tract infection (66.7%), headache (44.4%), alopecia (33.3%), and vertigo (33.3%)

Table 3. Safety Profile

	Participants, n (%)
At least 1 TEAE	9 (100.0)
Serious AEs	1 (11.1)
AEs leading to study withdrawal	1 (11.1)
Common AEs (≥20%)	
Upper respiratory tract infection	6 (66.7)
Headache	4 (44.4)
Alopecia	3 (33.3)
Vertigo	3 (33.3)
Gastroenteritis	2 (22.2)
Influenza	2 (22.2)
Fatigue	2 (22.2)
Upper abdominal pain	2 (22.2)
Hypoglycemia[a]	2 (22.2)

AE, adverse event; TEAE, treatment-emergent AE. [a]One participant with hypoglycemia had type 1 diabetes and was receiving insulin therapy.

- 1 serious adverse event (hypoglycemia) occurred in a participant with type 1 diabetes who was receiving insulin therapy
- A participant with POMC deficiency obesity voluntarily discontinued the study

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