Suicidality and Depression in Individuals With Genetic Obesity Treated With Setmelanotide

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Summary

- **Because of their severe obesity,[1-5] individuals with proopiomelanocortin (POMC)/proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency may be at a higher risk for experiencing depression and/or suicidal ideation**
- **Psychological evaluation and support are thus important for participants, given the severe disease burden**
- **In these phase 3 trials, there was no treatment-related effect of setmelanotide on depression or suicidality. Treatment was well tolerated and associated with weight loss**

Introduction

- Rare genetic variants in *POMC*, *PCSK1*, and *LEPR* impair signaling in the central melanocortin pathway, resulting in early-onset severe obesity and insatiable hunger[6,7]
- Individuals with obesity are at increased risk of depression and suicidal ideation[1-5]
  - However, little is known about these risks in individuals with POMC/PCSK1 or LEPR deficiency obesity
- Neuropsychiatric adverse events (AEs), including depression and suicidal ideation, have been documented with some centrally acting obesity drugs[8]
- Setmelanotide is a melanocortin-4 receptor agonist that has been shown to reduce body weight and hunger scores in 2 phase 3 trials of individuals with POMC/PCSK1 and LEPR deficiency obesity[9,10]
- In both phase 3 trials, setmelanotide was well tolerated
  - The most common AEs were injection site reaction, skin hyperpigmentation, and nausea/diarrhea/vomiting

Objective

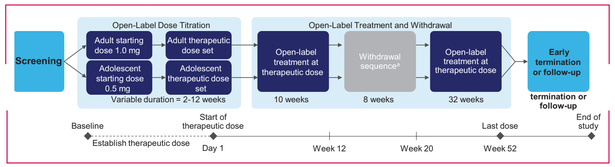
- To examine baseline indices of depression and suicidality in individuals with POMC/PCSK1 or LEPR deficiency obesity
- To determine if the centrally acting melanocortin-4 receptor agonist setmelanotide affects depression and suicidality indices in individuals with POMC/PCSK1 or LEPR deficiency obesity

Methods

Study Design

- These 2 open-label, multicenter, placebo-controlled, phase 3 clinical trials assessed the efficacy and safety of daily setmelanotide in participants with POMC/PCSK1 (NCT02896192) or LEPR deficiency obesity (NCT03287960; Figure 1)

Figure 1. Study design.



[a]Participants with ≥5 kg weight loss (or ≥5% if weighing <100 kg at baseline) entered an 8-week double-blind placebo-controlled withdrawal sequence (including 4 weeks of placebo) followed by 32 weeks of open-label treatment. Participants who did not achieve the weight loss threshold were not included in the placebo period.

- Participants first entered a dose-titration phase to determine individualized therapeutic doses of setmelanotide and then entered a 10-week, open-label treatment phase after establishment of the therapeutic dose (the final 2 weeks of dose titration phase are at the therapeutic dose)
- Participants who lost ≥5 kg (or ≥5% if weighing <100 kg at baseline) in the open-label treatment phase entered an 8-week double-blind placebo-controlled withdrawal phase, inclusive of 4 weeks of placebo and 4 weeks of setmelanotide, and then resumed setmelanotide at the therapeutic dose for an additional 32 weeks

Key Inclusion Criteria

- All participants had homozygous or compound heterozygous variants in *POMC*, *PCSK1*, or *LEPR*
- Adults (aged ≥18 years) had a body mass index of ≥30 kg/m^2; children or adolescents (aged ≥6 years to <18 years) had a weight >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
- Participants were also excluded if they had a Patient Health Questionnaire-9 (PHQ-9) score of ≥15, any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS), any lifetime history of a suicide attempt, or any suicidal behavior in the last month

Endpoints and Assessment

- Changes in depression and suicidality were evaluated using the PHQ-9 and C-SSRS (standard [age ≥12] or children's [age <12] questionnaire), respectively
- Herein, "study week" refers to the time on study according to the protocol schedule of assessments; relative calendar weeks may vary for each participant depending on the duration of the dose titration phase
  - Study week 2 refers to the start of the treatment phase

Results

Participant Disposition and Baseline Characteristics

- These trials enrolled 9 participants with POMC deficiency obesity (aged 11 to 30 years), 1 participant with PCSK1 deficiency obesity (aged 11 years), and 11 participants with LEPR deficiency obesity (aged 12 to 37 years; Table)
  - A total of 18 participants, 9 participants (90% [N=10]) with POMC/PCSK1 deficiency obesity and 9 participants (82% [N=11]) with LEPR deficiency obesity, completed the trials

Table. Baseline Participant Characteristics

	POMC/PCSK1 (N=10)	LEPR (N=11)
Genotype, n (%)		
POMC compound heterozygous	2 (20)	
POMC homozygous	7 (70)	
PCSK1 homozygous	1 (10)	
LEPR compound heterozygous		6 (55)
LEPR homozygous		5 (45)
Age, mean (SD) [range], y	18.4 (6.2) [11–30]	23.4 (8.7) [12–37]
Male, n (%)	5 (50)	3 (27)
Ethnicity, n (%)		
Hispanic or Latino	1 (10)	0 (0)
Not Hispanic or Latino	8 (80)	11 (100)
Unknown	1 (10)	0 (0)
Weight, mean (SD) [range], kg	118.7 (37.5) [55.9–186.7]	133.3 (26.0) [89.4–170.4]
BMI, mean (SD) [range], kg/m^2	40.4 (9.1) [26.6–53.3]	48.2 (10.5) [35.8–64.6]
Most hunger score, mean (SD) [range][a]	8.0 (0.75) [7–9]	7.1 (1.0) [5–8]
Depression level (age ≥12), mean (SD)[b]	7.1 (3.7)	3.4 (3.0)
Suicidal ideation (age ≥12), n (%)[c]	0 (0)	2 (29)
Suicidal ideation (age <12), n (%)[c]	1 (17)	NR

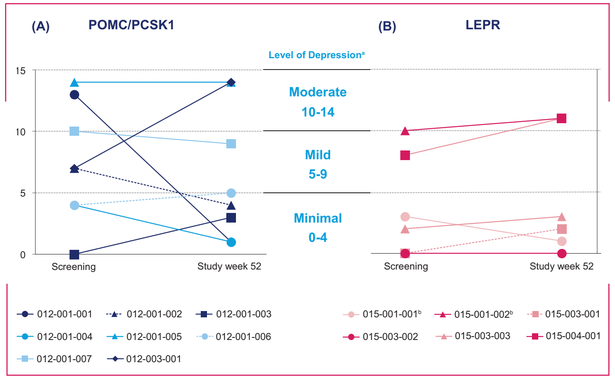
BMI, body mass index; LEPR, leptin receptor; NR, not reported; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SD, standard deviation. [a]Most hunger score in individuals ≥12 years old was determined on a 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" [b]Based on Patient Health Questionaire-9 total score. [c]Based on Columbia Suicide Severity Rating Scale standard questionnaire (POMC/PCSK1: n=3; LEPR: n=7). [d]Based on Columbia Suicide Severity Rating Scale children's questionnaire (POMC/PCSK1: n=6).

- At screening, participants reported moderate (4/19), mild (6/19), or no depression (9/19), with an average depression level (PHQ-9 score) in the POMC/PCSK1 and LEPR trials of 7.1 and 3.4, respectively
- Also at screening, 1 participant aged <12 years (1/6; 17%) in the POMC/PCSK1 trial and 2 participants aged ≥12 years (2/7; 29%) in the LEPR trial reported suicidal ideation. Intermittent suicidal ideation continued throughout the trial, unrelated to treatment with setmelanotide

Outcomes

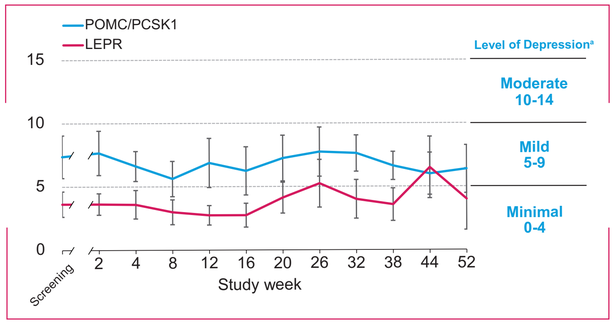
- 7 participants (POMC/PCSK1, 4; LEPR, 3) experienced serious AEs (none related to treatment)
  - 2 POMC/PCSK1 participants (012-001-001 and 012-006-001) experienced depression and 1 LEPR participant (015-002-003) experienced suicidal ideation; none of these events required treatment interruption
  - Depressive episodes likely stem from the burden of the disease and the difficult situation for the patient and family due to persistent hyperphagia and weight gain
- Overall individual PHQ-9 scores showed no worsening of depression over time (Figure 2), and average scores also remained statistically unchanged (least squares mean percent change from screening to study week 52: POMC/PCSK1, −12.43% [n=7; *P*=0.2882]; LEPR, −0.44% [n=6; *P*=0.4938]) (Figure 3)

Figure 2. Individualized participant changes in level of depression during the trials as determined by the PHQ-9 score for participants with **(A)** POMC/PCSK1 or **(B)** LEPR deficiency obesity.



LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; PHQ-9, Patient Health Questionaire-9; POMC, proopiomelanocortin. [a]Participants were excluded at screening if they had a PHQ-9 score ≥15; therefore, depression levels of severe (20–27) and moderately severe (15–19) are not shown. Level of depression based on.[11] [b]Assessment at study week 56.

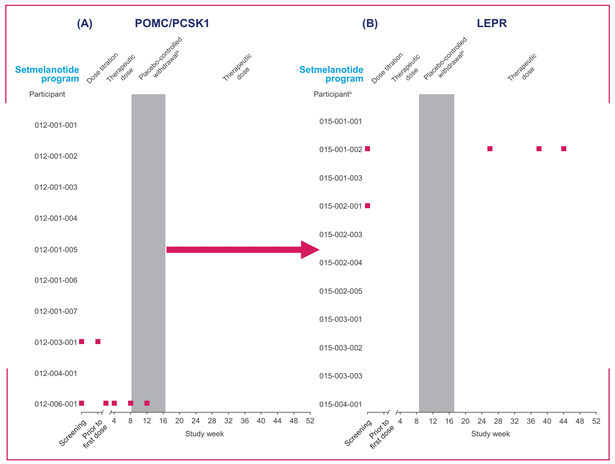
Figure 3. Average level of depression as determined by the PHQ-9 score for participants with POMC/PCSK1 (blue line) or LEPR (red line) deficiency obesity.



LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; PHQ-9, Patient Health Questionaire-9; POMC, proopiomelanocortin. Error bars are the standard error of the mean. [a]Participants were excluded at screening if they had a PHQ-9 score ≥15; therefore, depression levels of severe (20–27) and moderately severe (15–19) are not shown. Level of depression based on.[11]

- There was no consistent increase in suicidal ideation or behavior with setmelanotide in either trial
- Health care providers reported some patients feeling burdened by the disease, dissatisfied with themselves, and anxious to fail
- In the POMC/PCSK1 trial, 3 participants reported suicidal ideation on the C-SSRS at any point on study (1 prior to treatment initiation only); 1 participant reported suicidal behavior that resolved (Figure 4)
  - A child participant (012-006-001) reported intermittent suicidal ideation usually without specific intent or plan during the study and reported suicidal behavior (superficial marks on wrist, self-interrupted attempt) during the placebo period (experienced weight gain). The participant was hospitalized for depression during the placebo withdrawal period
  - An adult participant (012-003-001) had a history of depression and indicated transient, infrequent, easily controlled suicidal ideation without suicidal behavior at screening and prior to the first dose of setmelanotide in the dose titration phase
  - Another adult participant (012-001-005) had a history of an adjustment disorder being treated with fluvoxamine. During study week 20 and for the remainder of the study, responses to C-SSRS assessments indicated transient, infrequent, easily controlled suicidal ideation without suicidal behavior. The treatment-emergent AEs associated with these findings were not considered related to treatment
- 3 participants with LEPR deficiency reported suicidal ideation at any point on study (1 at screening only); no suicidal behavior was reported
  - An adult participant (015-001-002) reported intermittent suicidal ideation without specific intent or plan at screening and during the study. The participant had nonspecific, transient suicidal thoughts that were easily controlled
  - Another adult participant (015-002-001) reported suicidal ideation at screening only
  - A third adult participant (015-002-003) had episodes of suicidal ideation during the study, coinciding with other life events (a death in the family and failed gastric band removal); the serious AE was not considered treatment related

Figure 4. Instances of suicidal ideation during the trials as determined by the C-SSRS for participants with **(A)** POMC/PCSK1 or **(B)** LEPR deficiency obesity.



C-SSR, Columbia Suicide Severity Rating Scale; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin. [a]Participants with ≥5 kg weight loss (or ≥5% if weighing <100 kg at baseline) entered an 8-week double-blind placebo-controlled withdrawal sequence (including 4 weeks of placebo received either in the first 4 weeks or second 4 weeks of the withdrawal phase; gray shading indicates full period where placebo could have been received). [b]Participant 15-002-003 experienced suicidal ideation at relative study days 309 and 350, which are within the reported study period, but were recorded as unscheduled visits.

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References: 1. Dutton GR et al. *Int J Obes (Lond).* 2013;37:1282-1286. **2.** Luppino FS et al. *Arch Gen Psychiatry.* 2010;67:220-229. **3.** Pereira-Miranda E et al. *J Am Coll Nutr.* 2017;36:223-233. **4.** Rao WW et al. *J Affect Disord.* 2020;267:78-85. **5.** Zeller MH et al. *Obesity (Silver Spring).* 2013;21:1039-1045. **6.** Huvenne H et al. *Obes Facts.* 2016;9:158-173. **7.** Yazdi FT et al. *PeerJ.* 2015;3:e856. **8.** Nathan PJ et al. *CNS Neurosci Ther.* 2011;17:490-505. **9.** Clément K et al. Poster presented at: ObesityWeek; November 3-7, 2019; Las Vegas, NV. **10.** Van Den Akker E et al. Poster presented at: ObesityWeek; November 3-7, 2019; Las Vegas, NV. **11.** Kroenke K et al. *J Gen Intern Med.* 2001;16:606-613.