Weight Category Improvement Following Setmelanotide in Patients With Acquired Hypothalamic Obesity

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Background

- Acquired hypothalamic obesity (aHO) is characterized by accelerated and sustained weight gain following injury to the hypothalamus[1-3]
- In the Phase 3 trial of the melanocortin-4 receptor (MC4R) agonist setmelanotide in aHO (NCT05774756), the primary endpoint of percent change in body mass index (BMI) at Week 52 was met[4]

Objective

- To examine changes in weight category in participants after 1 year of setmelanotide treatment or placebo

Methods

- Participants aged ≥4 years with BMI ≥95th percentile (4 to <18 years) or ≥30 kg/m^2 (≥18 years) with aHO following hypothalamic tumor, lesion, or injury were included and randomized 2:1 to setmelanotide or placebo for up to 60 weeks[4]
  - For this analysis, participants with an observed primary endpoint value at 52 weeks on therapeutic regimen were included
  - Changes in BMI (in those aged ≥18 years) and percent of the 95th BMI percentile (%BMI95; in those aged <18 years) from baseline to 1 year of treatment were assessed and stratified by respective weight categories (Table 1)

Table 1. Adult and Pediatric Weight Categories[5-7]

Weight category	Pediatric (<18 y), BMI percentile	Adult (≥18 y), BMI kg/m^2
Class III obesity	%BMI95 ≥140%	≥40
Class II obesity	%BMI95 ≥120% to <140%	≥35 to <40
Class I obesity	BMI ≥95th to %BMI95 <120%	≥30 to <35
Overweight	≥85th to <95th	≥25 to <30
Healthy	≥5th to <85th	18.5 to <25

BMI, body mass index; %BMI95, percent of the 95th BMI percentile.

Table 2. Baseline Demographics

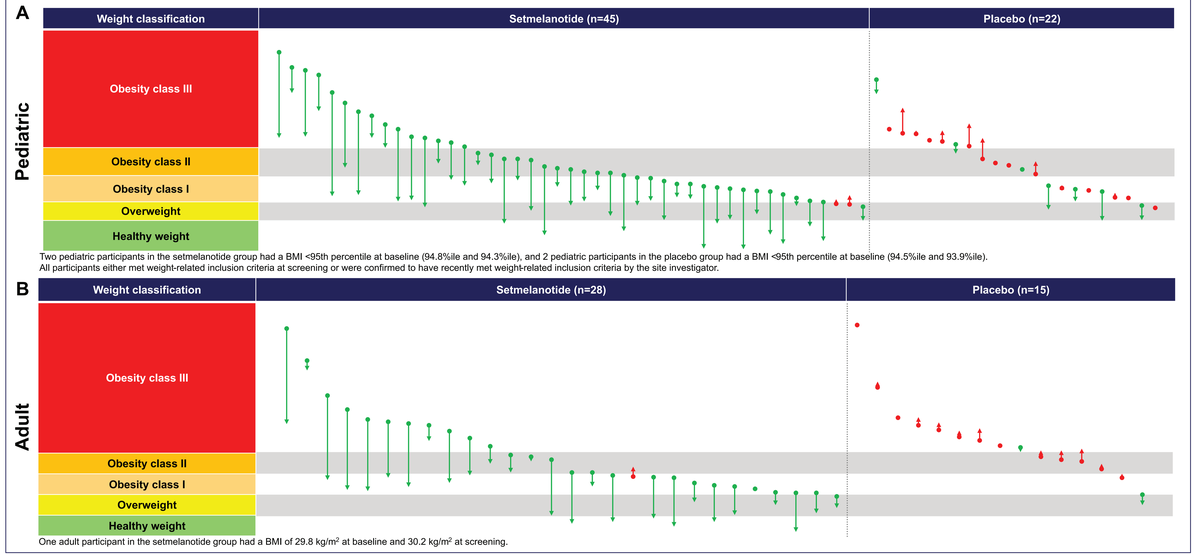
	SET (n=81)	PBO (n=39)
Age, mean ± SD (range), y	19.2 ± 13.0 (4-65)	21.4 ± 15.5 (4-66)
Age <18 y, n (%)	48 (59.3)	23 (59.0)
Age ≥18 y, n (%)	33 (40.7)	16 (41.0)
Sex, female, n (%)	45 (55.6)	27 (69.2)
Race, n (%)		
White	66 (81.5)	34 (87.2)
Black/African American	6 (7.4)	0
Asian	3 (3.7)	0
Other	6 (7.4)	5 (12.8)
Weight, mean (SD), kg	92.9 (38.5)	94.1 (38.8)
In participants aged ≥18 y, kg	115.6 (33.8)	124.2 (32.9)
BMI, mean (SD), kg/m^2	35.7 (9.2)	36.8 (9.3)
In participants aged ≥18 y, kg/m^2	40.1 (9.8)	43.5 (9.3)
BMI z-score in participants aged 4 to <18 y, mean (SD)*	3.72 (1.81)	3.37 (1.29)
%BMI95 in participants aged 4 to <18 y, mean (SD)†	132.3 (28.9)	128.6 (22.7)

%BMI95, percent of the 95th BMI percentile; PBO, placebo; SD, standard deviation; SET, setmelanotide.
*BMI z-score calculated according to the World Health Organization 2007 method.
†Percentage of the 95th percentile of BMI calculated according to the Centers for Disease Control and Prevention 2022 method.

Results

- Of the 120 total participants in the pivotal cohort, 71 were <18 years old and 49 were ≥18 years old (Table 2)
  - Overall, 110 participants had an observed BMI value at baseline and at 52 weeks on therapeutic regimen (67, <18 years old; 43, ≥18 years old) and were included in this analysis
- At baseline, 40 of 67 pediatric participants (59.7%) and 29 of 43 adult participants (67.4%) had class II or III obesity
- After 1 year, improvements of ≥1 weight category were observed in 32 of 45 pediatric (71.1%) and 20 of 28 adult (71.4%) participants treated with setmelanotide (Figure 1)
  - Improvements of ≥2 weight categories were observed in 20 of 45 pediatric participants (44.4%) and 14 of 28 adults (50.0%)
- By contrast, after 1 year, for the placebo group, 3 of 22 pediatric (13.6%) and 1 of 15 adult (6.7%) participants improved ≥1 weight category
  - No participant at any age improved ≥2 weight categories in the placebo group

Figure 1. Individual changes in weight category with setmelanotide treatment versus placebo in (A) pediatric and (B) adult participants.



Two pediatric participants in the setmelanotide group had a BMI <95th percentile at baseline (94.8%ile and 94.3%ile), and 2 pediatric participants in the placebo group had a BMI <95th percentile at baseline (94.5%ile and 93.9%ile).
All participants either met weight-related inclusion criteria at screening or were confirmed to have recently met weight-related inclusion criteria by the site investigator.

One adult participant in the setmelanotide group had a BMI of 29.8 kg/m^2 at baseline and 30.2 kg/m^2 at screening.

- After 1 year, 32 of 73 participants (43.8%) receiving setmelanotide achieved either overweight or healthy weight status, whereas 5 of 37 participants (13.5%) receiving placebo achieved overweight (none had healthy weight)
- Common adverse events reported in >30% of the setmelanotide group were skin hyperpigmentation (setmelanotide, 55.6%; placebo, 7.7%), nausea (setmelanotide, 50.6%; placebo, 30.8%), vomiting (setmelanotide, 39.5%; placebo, 17.9%), and headache (setmelanotide, 38.3%; placebo, 30.8%; Table 3)

Table 3. Safety

n (%)	SET (n=81)	PBO (n=39)
Adverse events	81 (100)	35 (89.7)
Any adverse event leading to treatment discontinuation	6 (7.4)	3 (7.7)
Any adverse event leading to study discontinuation	4 (4.9)	0
Serious adverse events	23 (28.4)	3 (7.7)
Adverse events resulting in death on study	1 (1.2)	0
Adverse events in ≥20% in the setmelanotide group		
Skin hyperpigmentation	45 (55.6)	3 (7.7)
Nausea	41 (50.6)	12 (30.8)
Vomiting	32 (39.5)	7 (17.9)
Headache	31 (38.3)	12 (30.8)
Injection site reaction	19 (23.5)	9 (23.1)
Diarrhea	19 (23.5)	8 (20.5)
Adverse events related to treatment*	71 (87.7)	26 (66.7)
Serious adverse events related to treatment*	1 (1.2)	0

PBO, placebo; SET, setmelanotide.
*Relatedness to treatment was assessed by the investigator.

Conclusion

- Most pediatric and adult participants treated with setmelanotide for 1 year exhibited an improvement in weight category, underscoring the importance of targeting the deficiency in MC4R signaling in aHO to allow patients to achieve a healthier BMI

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