Weight Reduction in Patients With Hypothalamic Obesity Treated With Setmelanotide for 12 Months

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Summary

- **Twelve months of treatment with setmelanotide resulted in meaningful changes in weight-related measures among a heterogeneous population of patients with hypothalamic obesity (HO)**

Introduction

- HO is an acquired form of obesity characterized by rapid weight gain following insult to the hypothalamus[1-3]
  - Damage to the hypothalamus resulting from tumor invasion, radiotherapy, or surgical resection can impair signaling in the melanocortin-4 receptor (MC4R) pathway, thus contributing to the cause of HO[1-3]
- Patients with HO are typically refractory to traditional weight management strategies[1,2]
- In a Phase 2 trial of setmelanotide, an MC4R agonist, patients with HO experienced clinically meaningful reductions in body weight and hunger after 16 weeks of treatment[4]
  - All adherent patients (n=17) experienced weight loss at Week 16
  - The mean percent change in body mass index (BMI) at Week 16 was −14.5% (n=17)

Objective

- To report changes in weight-related parameters after 12 months of setmelanotide treatment in patients with HO who entered a long-term extension (LTE) trial

Methods

Study design

- Patients aged 6-40 years from a Phase 2 multicenter, open-label trial of setmelanotide (NCT04725240) were eligible to enroll in an LTE trial (NCT03651765) if they experienced ≥5% BMI reduction or investigator-determined clinically meaningful benefit and exhibited adequate safety after 16 weeks of treatment
- During the index trial, the setmelanotide dose was titrated over 2-4 weeks to a maximum of 3.0 mg administered once daily via subcutaneous injection for a total of 16 weeks of treatment
- During the LTE, setmelanotide was administered at the dose established during the index trial

Outcomes

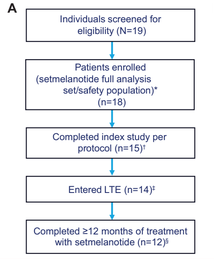
- This analysis assessed the following outcomes at Month 12:
  - Individual BMI percent change from baseline
  - Mean BMI percent change from baseline in adult (aged ≥18 years) and pediatric (aged <18 years) patients
  - Mean BMI Z score and percent of the 95th percentile for BMI (%BMI95) change from baseline in pediatric patients
  - Frequency of adverse events (AEs)
- Mean body composition changes from baseline to Week 16 and ≥1 year (ie, between days 366 and 730) were also assessed

Results

Patient disposition and baseline characteristics

- Of 18 patients who enrolled in the index trial, 14 (77.8%) continued into the LTE and 12 (66.7%) had received ≥12 months of setmelanotide at the time of the analysis (Figure 1A)
  - Most patients enrolled in the LTE (n=14) were aged <18 years at study entry and received treatment for craniopharyngioma; mean (standard deviation [SD]) weight and BMI at baseline were 99.1 (32.7) kg and 37.0 (7.1) kg/m^2, respectively (Figure 1B)

Figure 1. (A) Patient disposition and **(B)** demographics and baseline characteristics.



B

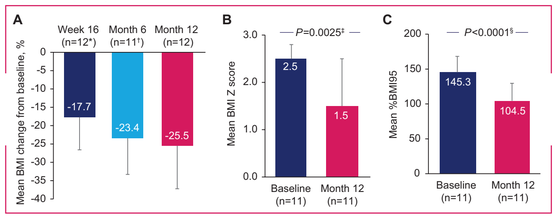
	Total (n=14)
Age, mean (SD), y	13.6 (5.0)
Age range, n (%), y	
Adults >18	2 (14.3)
Children 10-18	12 (85.7)
Sex, n (%)	
Female	4 (28.6)
Male	10 (71.4)
Tumor type, n (%)	
Craniopharyngioma	11 (78.6)
Hypothalamic hamartoma	2 (14.3)
Juvenile pilocytic astrocytoma	1 (7.1)
Waist circumference, mean (SD), cm	112.0 (17.9)
Weight, mean (SD), kg	99.1 (32.7)
BMI, mean (SD), kg/m^2	37.0 (7.1)
BMI Z score, mean (SD)¶	2.5 (0.3)
%BMI95, mean (SD)#	145.3 (22.8)

*Screen failure (n=1). †Two patients discontinued because of an AE and 1 patient was nonadherent to study drug administration. ‡One patient was diagnosed with *Clostridioides difficile* colitis during the index trial and did not enter the LTE trial. ‖One patient was lost to follow-up and off treatment, then reconsented and re-entered the trial at Month 12. One patient discontinued setmelanotide before Month 12 because of an AE but remained in the trial. ¶BMI Z score was calculated for patients aged <18 years (n=11) using the Centers for Disease Control and Prevention 2022 methodology. #Based on 11 pediatric patients. AE, adverse event; %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; LTE, long-term extension; SD, standard deviation.

Efficacy outcomes

- The mean percent change in BMI from baseline to Month 12 in adult and pediatric patients was −25.5% (Figure 2A)
  - In pediatric patients (n=11), the mean change in BMI Z score from baseline to Month 12 was −1.1 and the mean change in %BMI95 was −40.7 percentage points (Figure 2B-C)

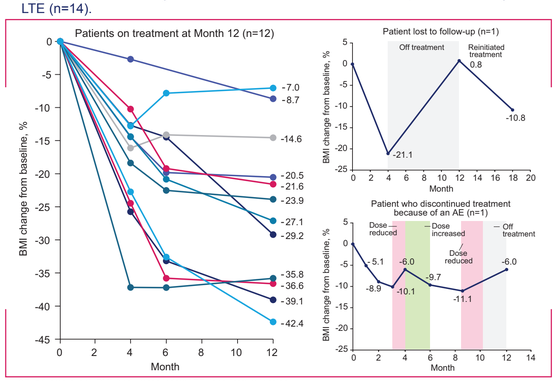
Figure 2. Changes in BMI, BMI Z score, and %BMI95 from index trial baseline over time. **(A)** Mean percent change in BMI from baseline at Week 16, Month 6, and Month 12 in adult and pediatric patients (n=12). **(B)** Mean BMI Z score at baseline and Month 12 in pediatric patients (n=11). **(C)** Mean %BMI95 at baseline and Month 12 in pediatric patients (n=11).



Error bars are the standard deviation. *Includes all patients who received 16 weeks of setmelanotide in the index trial and ≥12 months of treatment in the long-term extension. †One patient did not complete a Month-6 visit. ‡One sample *t*-test with 2-tailed *P*-values. §Paired *t*-test with 2-tailed *P*-values. BMI, body mass index; %BMI95, percent of the 95th percentile for BMI.

- All patients experienced ≥5% BMI reduction from index trial baseline to Month 12 (Figure 3)
  - One patient who was lost to follow-up and discontinued setmelanotide immediately after entering the LTE had a −21.1% change in BMI from baseline to Week 16 during the index trial and a +0.8% change in BMI from baseline when they reconsented and re-entered the LTE at Month 12; after reinitiating setmelanotide treatment, they had a −10.8% change in BMI from baseline at Month 18 (Figure 3)
  - The patient who discontinued setmelanotide because of an AE had a −9.7% change in BMI from index trial baseline to Month 6 of the LTE before discontinuing setmelanotide; after discontinuing, this patient had a −6.0% change in BMI from baseline at Month 12 (Figure 3)

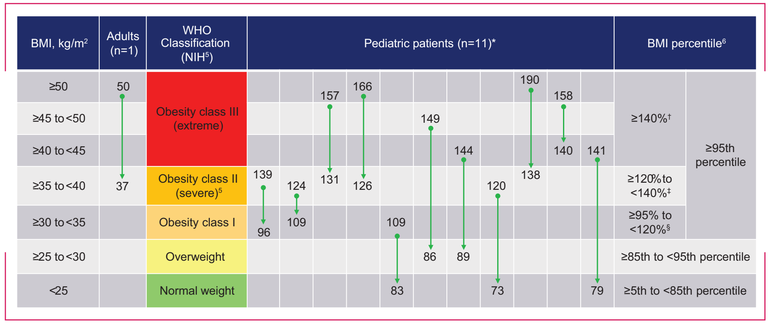
Figure 3. Percent changes in BMI from index trial baseline in all patients entering the LTE (n=14).



AE, adverse event; BMI, body mass index; LTE, long-term extension.

- All patients experienced a decrease in the severity of obesity at Month 12 (Figure 4)
  - Eleven of 12 patients (91.7%) improved by ≥1 weight class (based on BMI or BMI percentile); the remaining patient, who had obesity class III at baseline, had a 7.0% reduction in BMI from baseline and a 17.4–percentage point reduction in %BMI95 from baseline

Figure 4. Weight class change across individual participants from index trial baseline to Month 12.

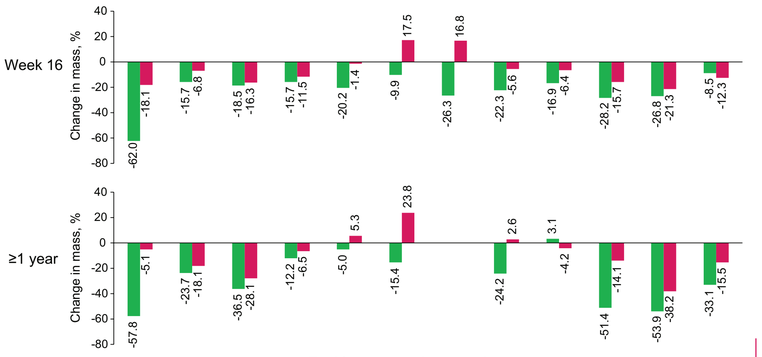


*Pediatric patients reported as %BMI95. †Or BMI ≥40 kg/m^2 (whichever is lower). ‡Or BMI ≥35 to <40 kg/m^2 (whichever is lower). §Or BMI ≥30 to <35 kg/m^2 (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; NIH, National Institutes of Health; WHO, World Health Organization.

- In adult and pediatric patients with body composition data at index trial baseline and ≥1 year (n=11), percent decreases in total fat mass were larger than percent decreases in lean muscle mass (Figure 5)
  - In pediatric patients (n=10), the mean (SD) percent change in total fat mass was −27.7% (21.4%; *P*=0.0027) and in lean muscle mass was −8.3% (17.6%; *P*=0.1704)
  - In the adult patient included in this analysis, total fat mass and lean muscle mass decreased by 33.1% and 15.5%, respectively

Figure 5. Body composition changes from index trial baseline to Week 16 and ≥1 year (ie, between days 366 and 730) in adult and pediatric patients (n=12).

Patient number	1	2	3	4	5	6	7	8	9	10	11	12
Age at baseline	6	9	9	10	11	12	13	14	15	15	16	24
Percent change in BMI from baseline to Month 12	-35.8	-20.5	-39.1	-23.9	-7	-8.7	-21.6	-29.2	-14.6	-36.6	-42.4	-27.1



BMI, body mass index.

Safety outcomes

- Of 14 patients who enrolled in the LTE, all had AEs of any causality during the index trial, and 11 (78.6%) had AEs of any causality during the LTE (Table)
  - During the index trial, the most frequent AEs among patients who later enrolled in the LTE were nausea (n/N=8/14; 57.1%), vomiting (n/N=4/14; 28.6%), and skin hyperpigmentation (n/N=4/14; 28.6%); during the LTE, these AEs were reported in 0, 2 (14.3%), and 0 patients, respectively
- There were no serious AEs, and no AEs led to study discontinuation during the index or LTE trial
- No new safety concerns were observed in the LTE

Table. AEs during the index and LTE trials for patients enrolled in the LTE (n=14)

AE	Index trial	LTE
Any	14 (100)	11 (78.6)
Related to study drug	12 (85.7)	6 (42.8)
Leading to temporary study drug interruption or dose decrease	2 (14.3)	5 (35.7)
Leading to study discontinuation	0	0
Serious	0	0
Resulting in death	0	0
Frequent (≥15%)		
Nausea	8 (57.1)	0
Vomiting	4 (28.6)	2 (14.3)
Skin hyperpigmentation	4 (28.6)	0
Injection site pain	3 (21.4)	0

AE, adverse event; LTE, long-term extension.

Conclusions

- At 12 months of setmelanotide treatment, the mean percent BMI decrease was 25.5%
- Most patients (91.7%) experienced ≥1 weight class improvement from baseline to Month 12, and 3 of 11 pediatric patients had normal weight at Month 12
- Body composition changes were favorable, with larger percent decreases in total fat mass compared with lean muscle mass
- Data from 1 patient who discontinued then reinitiated setmelanotide treatment during the LTE showed weight gain while off treatment followed by weight loss upon reinitiation of treatment
- The consistent and sustained clinical response to setmelanotide suggests an important role of the MC4R pathway in the pathophysiology of HO
- Setmelanotide may be a beneficial therapeutic option for a disease that has no approved therapies to date
- A randomized, double-blind, placebo-controlled, Phase 3 trial of setmelanotide in patients with HO (NCT05774756) is currently recruiting

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References: 1. Kim and Choi. *Ann Pediatr Endocrinol Metab.* 2013;18:161-167. **2.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **3.** Dimitri. *Front Endocrinol (Lausanne).* 2022;13:846880. **4.** Roth et al. Presented at: ObesityWeek; November 1-4, 2022; San Diego, CA. **5.** National Institutes of Health. *Obes Res.* 1998;6(suppl 2):51S-209S. **6.** Hampl et al. *Pediatrics.* 2023;151:e2022060640.