Weight-Related Measures in Pediatric 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 pediatric patients with acquired hypothalamic obesity (HO)**

Introduction

- Acquired HO is a form of obesity characterized by rapid weight gain after 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 acquired HO are typically refractory to traditional weight management strategies[1,2]
- In a Phase 2 trial of setmelanotide, an MC4R agonist, patients with acquired HO experienced clinically meaningful reductions in age-appropriate weight-related parameters and hunger after 16 weeks of treatment[4]
  - All pediatric patients (n=13) experienced weight loss at Week 16
  - Pediatric patients (n=13) exhibited a reduction from baseline across body mass index (BMI; −17.6%), BMI Z score (−1.3 points), and percent of the 95th BMI percentile (%BMI95; 27.0 percentage points)

Objective

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

Methods

Study design

- Patients aged 6 to 40 years from a Phase 2 multicenter, open-label, 16-week trial of setmelanotide (NCT04725240) were eligible to enroll in the 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 to 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 in pediatric patients (aged <18 years):
  - Individual BMI percent change from baseline
  - Mean BMI percent change from baseline
  - Mean BMI Z score (Centers for Disease Control and Prevention) and %BMI95 change from baseline
  - 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
- Significance was determined with a 1-sample *t* test with 2-sided *P* values

Results

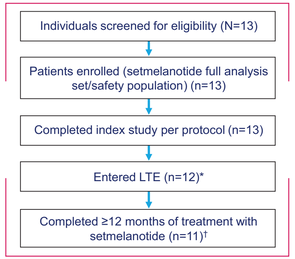
Patient disposition and baseline characteristics

- Of 13 pediatric patients who enrolled in the index trial, 12 (92%) continued into the LTE and 11 (85%) had received ≥12 months of setmelanotide at the time of the analysis (Figure 1)
  - Most pediatric patients enrolled in the LTE had received treatment for craniopharyngioma; mean (standard deviation [SD]) weight and BMI at baseline were 94.1 (31.4) kg and 35.9 (6.2) kg/m^2, respectively (Table 1)

Efficacy outcomes

- Overall, the mean (SD) percent change in BMI from baseline to Month 12 with uninterrupted treatment (n=11) was −25.4% (12.2%) (Figure 2A)
  - A reduction from baseline was observed at Month 12 for age-appropriate weight-based parameters across pediatric patients (n=11); the mean (SD) changes from baseline in BMI Z score and %BMI95 were −1.1 (0.9) points and −40.7 (17.1) percentage points, respectively (Figure 2B and C)
  - One patient had a −21.1% change in BMI from baseline to Week 16 during the index trial but was lost to follow-up and discontinued setmelanotide immediately after entering the LTE. The patient reconsented and reentered the LTE at Month 12, at which time, they exhibited a +0.8% change in BMI from baseline; after reinitiating setmelanotide treatment, they had a −10.8% change in BMI from baseline at Month 18 (Figure 2D)

Figure 1. Patient disposition.



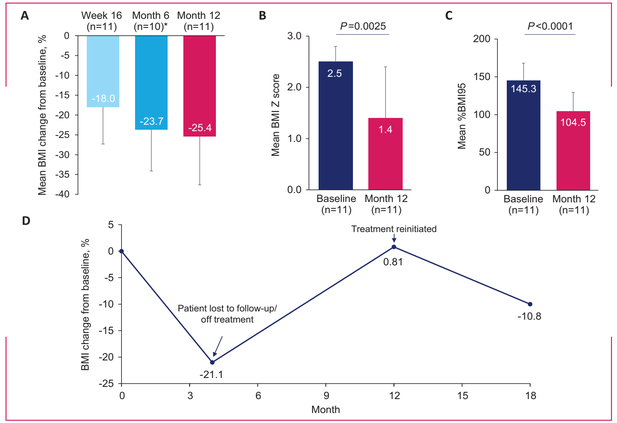
*1 patient was diagnosed with *Clostridioides difficile* colitis during the index trial and did not enter the LTE because of ongoing nausea and vomiting. †1 patient was lost to follow-up and off treatment but reconsented and reentered the trial at Month 12. LTE, long-term extension.

Table 1. Baseline Characteristics

Parameter	Total (n=12)
Age, mean (SD), y	11.9 (2.9)
Age range, y	6-16
Sex, n (%)	
Female	3 (25)
Male	9 (75)
Tumor type, n (%)	
Craniopharyngioma	10 (83)
Hypothalamic hamartoma	2 (17)
Waist circumference, mean (SD), cm	108.8 (16.0)
Weight, mean (SD), kg	94.1 (30.1)
BMI, mean (SD), kg/m^2	35.9 (6.2)
BMI Z score,* mean (SD)	4.0 (0.94)
%BMI95,* mean (SD)	145.8 (21.9)

*BMI Z score and %BMI95 were calculated for patients aged <18 years based on the Centers for Disease Control and Prevention 2022 methodology. %BMI95, percent of the 95th BMI percentile; BMI, body mass index; SD, standard deviation.

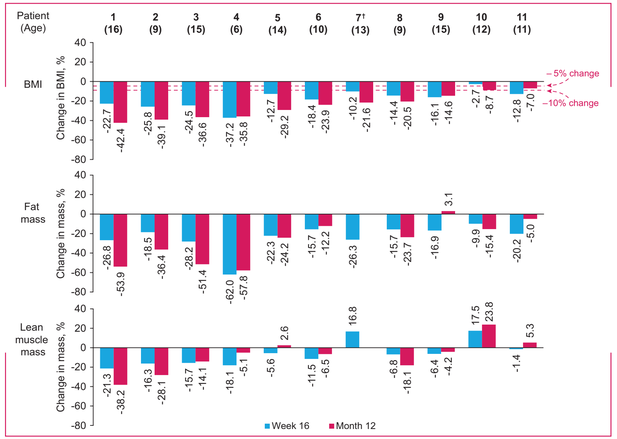
Figure 2. Changes in BMI, BMI Z score, and %BMI95 from index trial baseline over time. **(A)** Mean percent change in BMI (n=11). **(B)** Mean BMI Z score at baseline and Month 12 (n=11). **(C)** Mean %BMI95 at baseline and Month 12 (n=11). **(D)** Percent change in BMI across treatment in a single patient lost to follow-up (n=1).



Data shown represent 11 patients with 12 months of continuous treatment at the time of analysis. Error bars represent standard deviation.*One patient did not have BMI data at Month 6. %BMI95, percent of the 95th BMI percentile; BMI, body mass index.

- All 11 pediatric patients with continuous setmelanotide treatment experienced ≥5% BMI reduction and 9 experienced ≥10% BMI reduction from index trial baseline to Month 12 (Figure 3)
  - In pediatric patients with body composition data at index trial baseline and ≥1 year (n=10), percent decreases in total fat mass were larger than percent decreases in lean muscle mass (Figure 3)
  - 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)

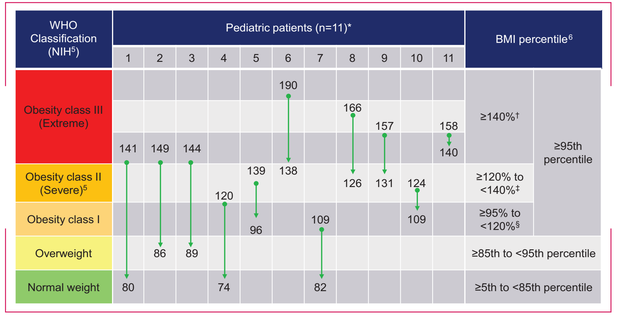
Figure 3. Individual BMI and body composition changes at Week 16 and ≥1 year.*



Patient numbers represent the same individual patient across figures. *Data presented are between days 366 and 730. †One patient did not have a 1+ year measurement for body composition. BMI, body mass index.

- All patients (n=11) experienced a decrease in the severity of obesity at Month 12 (Figure 4)
  - Ten of 11 patients (90.9%) with 12 months of continuous treatment 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. Individual weight class change from baseline to Month 12.



Patient numbers represent the same individual patient across figures. *Data reported as %BMI95. †Or BMI ≥40 kg/m^2 (whichever is lower). ‡Or BMI ≥35 to <40 kg/m^2 (whichever is lower).[3] §Or BMI ≥30 to <35 kg/m^2 (whichever is lower).[3] ¶%BMI95, percent of the BMI 95th percentile; BMI, body mass index; NIH, National Institutes of Health; WHO, World Health Organization.

Safety outcomes

- Of 12 pediatric patients who enrolled in the LTE, all had AEs of any causality during the index trial and 11 (92%) had AEs of any causality during the LTE (Table 2)
- During the index trial, the most frequent AEs among patients who later enrolled in the LTE were nausea (n/N=6/12; 50%), skin hyperpigmentation (n/N=5/12; 42%), increased frequency of penile erection in males (n/N=3/9; 33%), and vomiting (n/N=3/12; 25%); during the LTE, these AEs were reported in 0, 2 (17%), 4 (33%), and 2 (17%) patients, respectively
- Serious AEs were experienced by 2 patients (17%) during the LTE including 1 patient who experienced 1 instance each of an influenza A infection, malaise, and septic shock, and another patient who was lost to follow-up and experienced a recurrence of craniopharyngioma; all serious AEs were determined not related to study drug
- In this population of pediatric patients (n=12), no AEs led to study discontinuation during the index or LTE trial
- No new safety concerns were observed in the LTE

Table 2. AEs of All Pediatric Patients Entering the LTE

AE, n (%)	Index trial (n=12)	LTE (n=12)
Any	12 (100)	10 (83)
Related to or probably related to study drug	10 (83)	5 (42)
Leading to temporary study drug interruption/dose decrease	4 (33)	3 (25)
Leading to study discontinuation	0	0
Serious	1	2
Serious and related to study drug	0	0
Resulting in death	0	0
Frequent (≥15% in safety population of index trial)		
Nausea	6 (50)	0
Skin hyperpigmentation	5 (42)	1 (8)
Increased frequency of penile erection	3 (33)*	3 (33)*
Vomiting	3 (25)	1 (8)
Injection site pain	3 (25)	0
Headache	2 (17)	1 (8)
Diarrhea	2 (17)	0
COVID-19	2 (17)	1 (8)
Upper respiratory tract infection	2 (17)	2 (17)
Injection site pruritus	2 (17)	0

*Increased percentages represent male population (n=9). AE, adverse event; LTE, long-term extension.

Conclusions

- In a population of pediatric patients with acquired HO who demonstrated weight loss and adequate safety in a 16-week index trial, 12 months of setmelanotide treatment was associated with a mean percent BMI decrease of 25.4% and significant decreases in both mean BMI Z score and %BMI95
  - Most patients (90.9%; n=10/11) 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 acquired HO (NCT05774756) is ongoing

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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.