Weight Loss at 18 Months of Setmelanotide in 2- to <6-Year-Old Patients With Rare MC4R Pathway Diseases

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Introduction

- The hypothalamic melanocortin-4 receptor (MC4R) pathway regulates hunger, satiety, energy expenditure, and, consequently, body weight[1-9]
- Rare variants in MC4R pathway genes may impair MC4R signaling, leading to hyperphagia (an absence of satiety and pathologic, insatiable hunger accompanied by abnormal food-seeking behaviors) and early-onset, severe obesity, often beginning in the first years of life[10-14]
- Treatment with the MC4R agonist setmelanotide resulted in significant weight reduction in a pivotal Phase 3 open-label trial in patients aged 2 to <6 years with proopiomelanocortin (POMC) deficiency, leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome (BBS) at 1 year (primary time point)[15]

Objective

- To assess the continued efficacy and safety of 18 months of setmelanotide treatment in 2- to <6-year-old patients with MC4R pathway–associated obesity

Methods

Trial design

- Patients from a Phase 3 multicenter, open-label trial of setmelanotide (NCT04966741) who were considered likely to benefit from continued treatment remained on setmelanotide after Week 52 at bridging visits
- Key inclusion criteria included ages 2 to <6 years with the presence of symptoms or behaviors of hyperphagia and obesity (body mass index [BMI] ≥97th percentile for age and sex and body weight of ≥15 kg) due to biallelic *POMC* or *PCSK1* variants (POMC deficiency), biallelic *LEPR* variants (LEPR deficiency), or genetically confirmed BBS
- An initial dosage of subcutaneous setmelanotide 0.5 mg once daily was increased by 0.5 mg every 2 weeks as tolerated to a weight-based maximum (<20 kg: 0.5 mg/day; 20 to <30 kg: 1.0 mg/day; 30 to <40 kg: 1.5 mg/day; ≥40 kg: 2.0 mg/day) for a total of 52 weeks; setmelanotide was administered at a maximum tolerable dose throughout the bridging visits

Outcomes

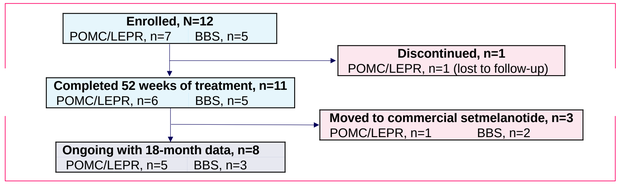
- BMI, BMI Z score (both Centers for Disease Control and Prevention [CDC] and World Health Organization [WHO] definitions), and percent of the BMI 95th percentile (%BMI95; CDC) from baseline to Month 18
- Safety and tolerability of setmelanotide, as assessed by the frequency and severity of adverse events (AEs)

Results

Patient disposition and baseline characteristics

- Of 11 patients who completed 52 weeks of setmelanotide treatment, 3 (27.3%) transitioned to commercial setmelanotide after turning 6 years old, and 8 (72.7%) continued setmelanotide treatment with bridging visits and had received ≥18 months of setmelanotide at the time of the analysis (May 2024; Figure 1)
- All patients had severe obesity at baseline, with BMI Z scores (CDC) ranging from 2.4 to 7.3 (Table 1)

Figure 1. Patient disposition.



BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; POMC, proopiomelanocortin.

Table 1. Baseline Demographics

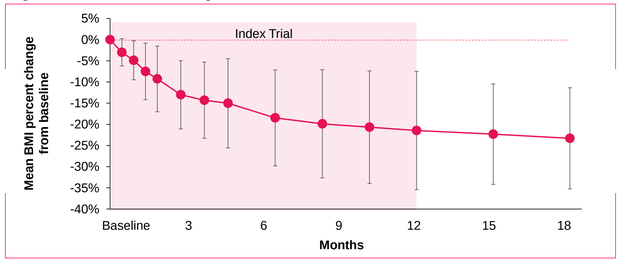
	POMC/LEPR deficiency	BBS	Total
Enrolled patients, n	5	3	8
Age range, y	3-4	2-4	2-4
Male, n (%)	4 (80.0)	2 (66.7)	6 (75.0)
Race, n (%)*			
White	2 (40.0)	3 (100.0)	5 (62.5)
Asian	-	-	-
Other	1 (20.0)	-	1 (12.5)
Not reported or unknown	2 (40.0)	-	2 (25.0)
Hispanic or Latino, n (%)	*	-	-
BMI, mean (SD), kg/m^2	34.8 (1.2)	21.7 (2.1)	29.0 (8.6)
BMI Z score, mean (SD)			
CDC	5.1 (1.7)	3.3 (0.81)	4.4 (1.5)
WHO	11.1 (2.1)	4.0 (1.2)	8.0 (4.7)
%BMI95, mean (SD)	193.7 (7.7)	119.7 (10.0)	161.2 (47.5)

*One patient not reported or unknown. BBS, Bardet-Biedl syndrome; BMI, body mass index; %BMI95, percent of the BMI 95th percentile; CDC, Centers for Disease Control and Prevention; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation; WHO, World Health Organization.

Efficacy outcomes

- Clinically meaningful reductions in age-appropriate weight measures were seen in all patients at 18 months of setmelanotide treatment
  - Mean reductions in weight measures were seen from baseline to Month 12, with continued and sustained reductions to Month 18
- The mean percent change from baseline in BMI was −23.3% at Month 18 (Figure 2)

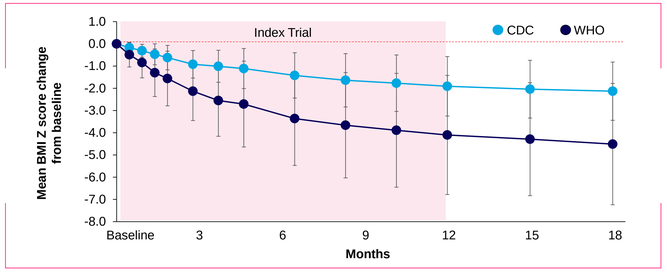
Figure 2. Percent BMI change from baseline.



Error bars are the standard deviation. BMI, body mass index.

- The mean change from baseline in BMI Z score was −2.1 (CDC) and −4.5 (WHO) at Month 18 (Figure 3)

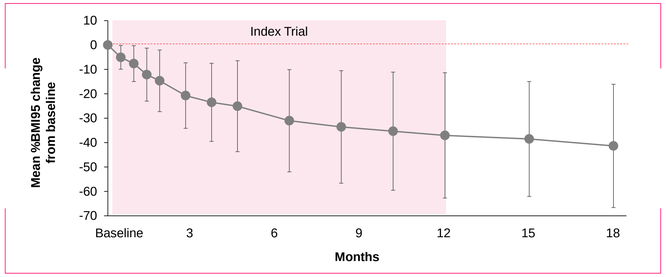
Figure 3. Mean BMI Z score (CDC and WHO) change from baseline.



Error bars are the standard deviation. BMI, body mass index; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

- The mean change from baseline in %BMI95 was −41.3 percentage points at Month 18 (Figure 4)

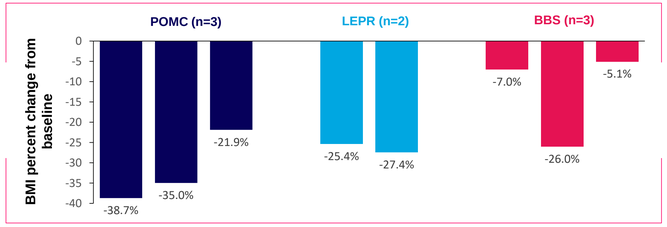
Figure 4. Mean %BMI95 (CDC) absolute percentage point reduction from baseline.



Error bars are the standard deviation. %BMI95, percent of the BMI 95th percentile; CDC, Centers for Disease Control and Prevention.

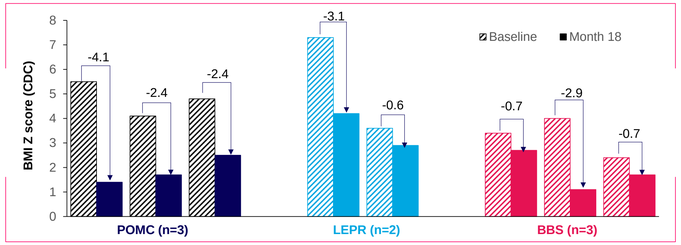
- Individual reductions in BMI percent change (Figure 5) and BMI Z score (CDC; Figure 6) were seen across all cohorts at Month 18

Figure 5. Individual BMI percent change from baseline by cohort at Month 18.



BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin.

Figure 6. Individual BMI Z scores (CDC) by cohort.



BBS, Bardet-Biedl syndrome; BMI, body mass index; CDC, Centers for Disease Control and Prevention; LEPR, leptin receptor; POMC, proopiomelanocortin.

Safety outcomes

- All patients had at least 1 AE and at least 1 treatment-related AE; skin hyperpigmentation (87.5%, all related to treatment) and nasopharyngitis (62.5%, all not related to treatment) were the most commonly reported AEs (Table 2)
- There were no deaths, serious AEs, or AEs leading to drug discontinuation
- There was no evidence of impaired growth or neurocognitive development

Table 2. Adverse Events

	POMC/LEPR deficiency (n=5), n (%)	BBS (n=3), n (%)	Total (N=8), n (%)
Any adverse event	5 (100.0)	3 (100.0)	8 (100.0)
Any treatment-related adverse event	5 (100.0)	3 (100.0)	8 (100.0)
Serious adverse event	0	0	0
Adverse event leading to drug discontinuation	0	0	0
Common adverse events in all patients (≥50%)			
Upper respiratory tract infection	4 (80.0)	0	4 (50.0)
Vomiting	3 (60.0)	1 (33.3)	4 (50.0)
Melanocytic nevus	3 (60.0)	1 (33.3)	4 (50.0)
Nasopharyngitis	2 (40.0)	3 (100.0)	5 (62.5)
Skin hyperpigmentation	5 (100)	2 (66.7)	7 (87.5)

Conclusions

- Patients 2 to <6 years of age with MC4R pathway diseases had severe obesity before setmelanotide
- Over 18 months of setmelanotide treatment, there were sustained, clinically meaningful reductions from baseline in all weight-related parameters, with no new safety concerns
  - Differences in degree of weight reduction between disease types may be due to variations in baseline severity and location of MC4R pathway dysfunction
- No approved therapies for patients <6 years old with rare MC4R pathway diseases currently exist in the United States, or for patients with general obesity globally, despite the need for early intervention with targeted therapy in these patients to reduce weight and potentially limit future comorbidities
  - Setmelanotide is authorized by the European Medicines Agency for patients with certain MC4R pathway diseases and is being reviewed by the United States Food and Drug Administration for this age group[16,17]
- On July 31, 2024, the European Commission expanded the marketing authorization for setmelanotide to include children between the ages of 2 and <6 years with obesity due to BBS or POMC (including variants in *PCSK1*) or LEPR deficiency; a supplemental new drug application has been submitted to the US Food and Drug Administration

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