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

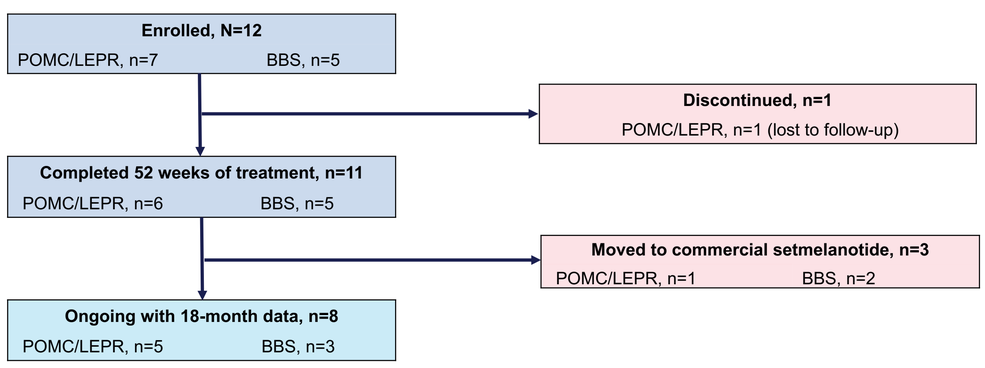


Table 1. Baseline demographics

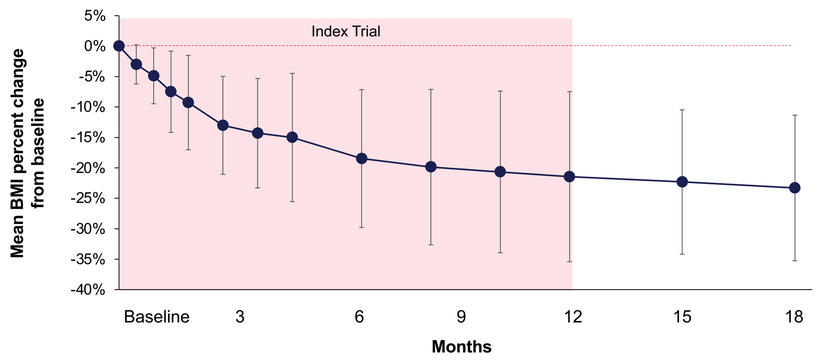
	POMC/LEPR deficiency	BBS	Total
Enrolled patients, n	5	3	8
Age range, y	3–4	2–4	2–4
Male, n (%)	4 (80.0)	2 (66.7)	6 (75.0)
Race, n (%)*			
White	2 (40.0)	3 (100.0)	5 (62.5)
Asian	-	-	-
Other	1 (20.0)	-	1 (12.5)
Not reported or unknown	2 (40.0)	-	2 (25.0)
Hispanic or Latino, n (%)	*	-	-
BMI, mean (SD), 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.
SD, standard deviation.

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)

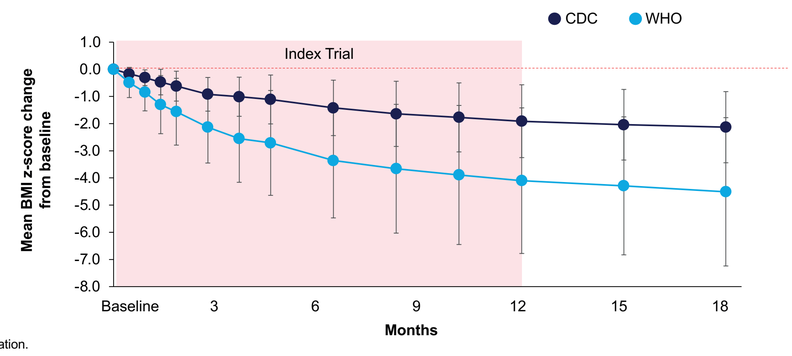
Figure 2. Percent BMI change from baseline



Error bars are the standard deviation.

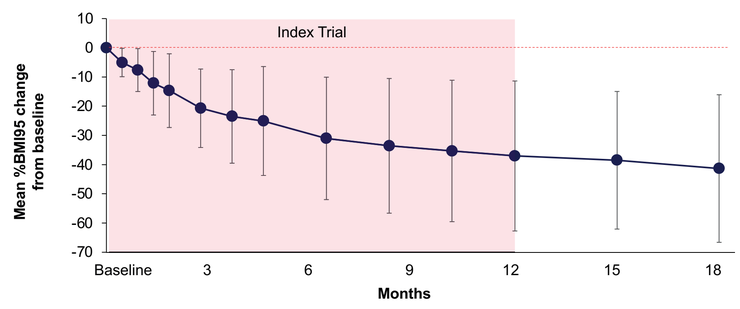
- The mean change from baseline in BMI z-score was −2.1 (CDC) and −4.5 (WHO) at Month 18 (Figure 3)

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



Error bars are the standard deviation.

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



Error bars are the standard deviation.

- 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

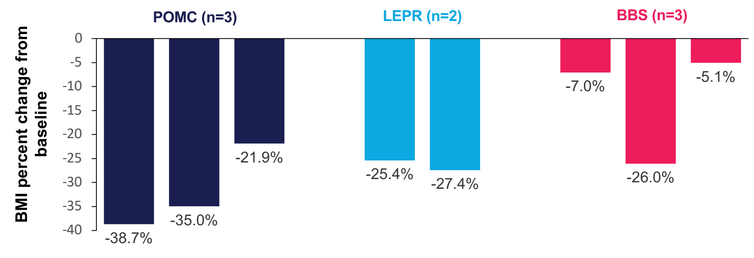
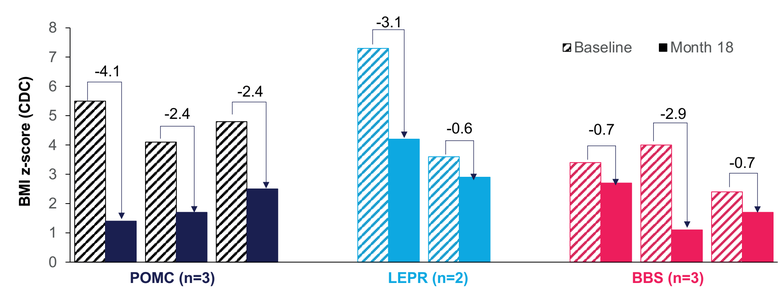


Figure 6. Individual BMI z-scores (CDC) by cohort



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
- Both the European Medicines Agency and the United States Food and Drug Administration have approved an expanded indication for setmelanotide to include children as young as 2 years old with obesity due to BBS or POMC (including variants in *PCSK1*) or LEPR deficiency

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