Evaluating Setmelanotide Treatment for 12 Months in Pediatric Age Groups With Rare Melanocortin-4 Receptor Pathway–Related Obesity: Efficacy in Weight Reduction and Safety Outcomes

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Background

- Under physiologic conditions, the hypothalamic melanocortin-4 receptor (MC4R) pathway regulates hunger, satiety, energy expenditure, and consequently body weight[1-4]
- 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[5-9]
  - This includes patients with proopiomelanocortin (POMC) deficiency, leptin receptor (LEPR) deficiency, and Bardet-Biedl syndrome (BBS)
- Acquired hypothalamic obesity (HO) is an acquired form of obesity characterized by rapid weight gain following insult to the hypothalamus[10-12]
- The MC4R agonist setmelanotide reduced body mass index (BMI) and hunger in clinical trials in pediatric patients aged 2-17 years in these populations and was well tolerated[13-18]
- Because this age range spans different developmental stages, further evaluation of the response to treatment or differences in adverse events (AEs) or events of special interest in refined age groups is important

Objective

- To report changes in weight-related measures and safety after 12 months of setmelanotide in patients stratified by age groups of 2-5, 6-11, and 12-17 years

Methods

Study design

- Patients aged 2-17 years who enrolled in 5 clinical trials of setmelanotide with
  - POMC deficiency (including variants in *PCSK1*; NCT02896192), LEPR deficiency (NCT03287960), BBS (NCT03746522), rare MC4R pathway diseases (2 to <6 years old; NCT04966741), and acquired HO (NCT04725240) who entered a long-term extension trial (NCT03651765) were included in this analysis
- Changes in BMI Z score (World Health Organization [WHO]) from index trial baseline after 12 months of setmelanotide were assessed
- Safety was evaluated by AE frequency

Results

Patient disposition and baseline characteristics

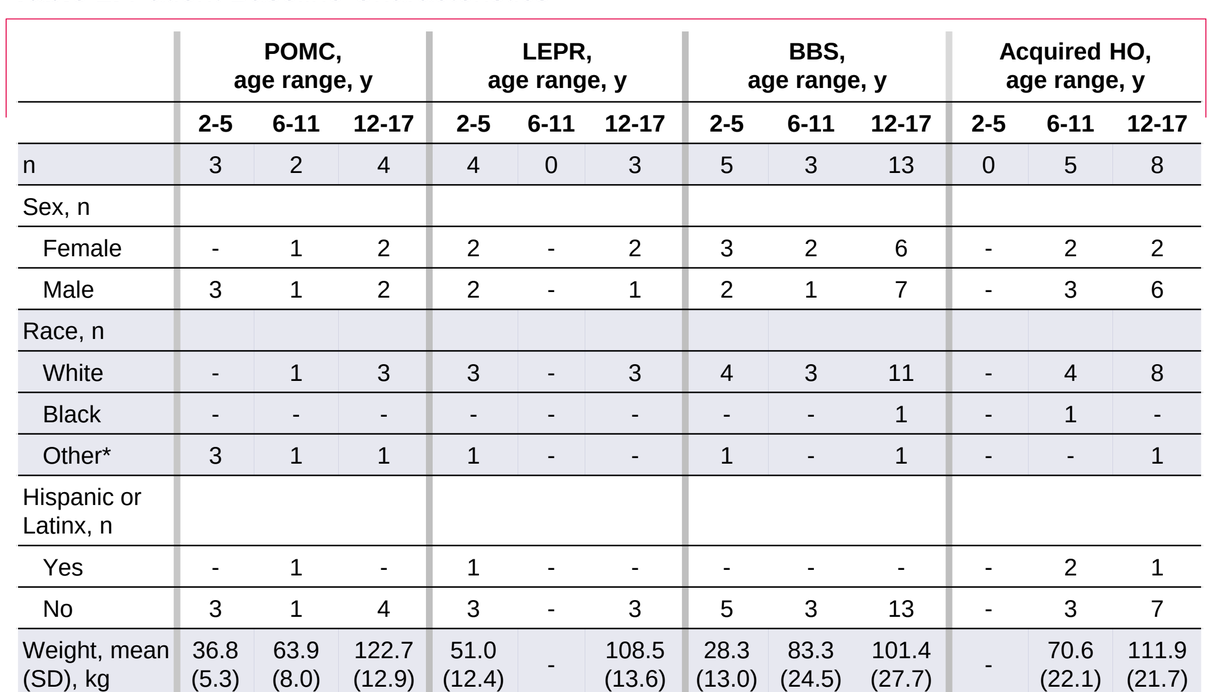
- A total of 50 pediatric patients were included in the analysis at baseline including those with POMC (n=9) or LEPR (n=7) deficiencies, BBS (n=21), and acquired HO (n=13; Table 1)

Table 1. Patient Baseline Characteristics

	POMC, age range, y			LEPR, age range, y			BBS, age range, y			Acquired HO, age range, y		
	2-5	6-11	12-17	2-5	6-11	12-17	2-5	6-11	12-17	2-5	6-11	12-17
n	3	2	4	4	0	3	5	3	13	0	5	8
Sex, n												
Female	-	1	2	2	-	2	3	2	6	-	2	2
Male	3	1	2	2	-	1	2	1	7	-	3	6
Race, n												
White	-	1	3	3	-	3	4	3	11	-	4	8
Black	-	-	-	-	-	-	-	-	1	-	1	-
Other*	3	1	1	1	-	-	1	-	1	-	-	1
Hispanic or Latinx, n												
Yes	-	1	-	1	-	-	-	-	-	-	2	1
No	3	1	4	3	-	3	5	3	13	-	3	7
Weight, mean (SD), kg	36.8 (5.3)	63.9 (8.0)	122.7 (12.9)	51.0 (12.4)	-	108.5 (13.6)	28.3 (13.0)	83.3 (24.5)	101.4 (27.7)	-	70.6 (22.1)	111.9 (21.7)
BMI Z score, mean (SD)	7.52 (0.63)	2.65 (0.01)	3.70 (0.30)	13.17 (2.85)	-	3.47 (0.31)	4.23 (0.96)	4.59 (1.05)	3.58 (1.32)	-	4.65 (0.84)	3.49 (0.52)

*Other includes Arabic, Moroccan, Middle Eastern, native Hawaiian/Pacific islander, Asian, or not reported. BBS, Bardet-Biedl syndrome; BMI, body mass index; HO, hypothalamic obesity; LEPR, leptin receptor deficiency; POMC, proopiomelanocortin deficiency; SD, standard deviation.

Figure. Mean BMI Z score reduction at 52 weeks.



BBS, Bardet-Biedl syndrome; BMI, body mass index; HO, hypothalamic obesity; LEPR, leptin receptor deficiency; NR, not reported; POMC, proopiomelanocortin deficiency. Given the small sample size, statistical comparisons were not performed between age subgroups.

Efficacy outcomes

- There were 5 patients who discontinued treatment before Week 52 (1 patient with LEPR deficiency was lost to follow-up, 2 patients with BBS and 2 patients with acquired HO discontinued because of AEs); the measurements of these patients are not included in Week-52 efficacy calculations
- The mean BMI Z score (WHO) was reduced from baseline in all groups, with greater reductions generally observed in younger age groups (Figure)

Safety outcomes

- Of the 50 patients, all had AEs of any causality during the 52-week period (Table 2)
- The most frequent AEs (≥40%) were skin hyperpigmentation (36/50; 72%), injection site erythema (22/50; 44%), vomiting (22/50; 44%), nausea (20/50; 40%), and injection site pruritus (20/50; 40%)
- AE frequency and severity did not differ substantially by age group, and there were no serious treatment-related AEs

Table 2. Adverse Events

	All, age range, y	POMC, age range, y			LEPR, age range, y			BBS, age range, y			Acquired HO, age range, y		
	2-17	2-5	6-11	12-17	2-5	6-11	12-17	2-5	6-11	12-17	2-5	6-11	12-17
No. of patients	50	3	2	4	4	-	3	5	3	13	-	5	8
Any AE	50 (100)	3	2	4	4	-	3	5	3	13	-	5	8
AE related to study drug	50 (100)	3	2	4	4	-	3	5	3	13	-	5	8
AE leading to dose interruption or decrease	17 (34)	2	2	1	1	-	0	1	1	3	-	2	4
AE leading to discontinuation	4 (8)	0	1	0	0	-	0	0	0	2	-	0	1
Serious treatment-related AE	0 (0)	0	0	0	0	-	0	0	0	0	-	0	0
AE resulting in death	0 (0)	0	0	0	0	-	0	0	0	0	-	0	0
AEs ≥25%, any causality													
Skin hyperpigmentation	36 (72)	3	2	4	2	-	3	4	2	10	-	1	5
Vomiting	22 (44)	2	0	4	2	-	0	3	2	5	-	1	3
Injection site erythema	22 (44)	0	2	4	0	-	3	2	2	8	-	0	1
Nausea	20 (40)	0	1	4	1	-	3	0	1	3	-	2	5
Injection site pruritus	20 (40)	0	2	2	1	-	2	3	2	6	-	0	2
Headache	16 (32)	0	1	2	0	-	2	1	1	6	-	1	2
COVID-19	15 (30)	0	0	1	2	-	3	0	0	5	-	1	3
Upper respiratory infection	15 (30)	3	1	4	1	-	1	0	0	1	-	2	2
Spontaneous erections	8 (29)*	1	0	0	0	-	0	0	1	1	-	0	5
Injection site induration	14 (28)	0	0	0	1	-	3	0	2	4	-	2	2
Injection site pain	13 (26)	0	0	1	0	-	1	1	2	5	-	1	2
Injection site bruising	13 (26)	1	2	0	0	-	2	3	2	3	-	0	0
AEs of special interest <25%													
Depression	5 (10)	0	1	0	0	-	2	0	0	2	-	0	0
Suicidal ideation	3 (6)	0	1	0	0	-	0	0	0	1	-	0	1
Melanocytic nevus	9 (18)	2	1	1	1	-	0	1	0	3	-	0	0

Values are the n or n (%). *Male patients only (n=28). AE, adverse event; BBS, Bardet-Biedl syndrome; HO, hypothalamic obesity; LEPR, leptin receptor deficiency; POMC, proopiomelanocortin deficiency.

- Serious AEs and AEs leading to study discontinuation or dose reduction during the 52 weeks occurred in 4 patients (2 BBS; 2 acquired HO)
  - A 12-year-old patient with BBS withdrew from the study at day 167 because of recurrence of AEs unrelated to the study drug (headaches, leg pain, and belligerent behavior)
  - Another 12-year-old patient with BBS experienced treatment-related AEs of nausea and vomiting that were moderate in intensity but led to treatment discontinuation on day 21
  - A 13-year-old patient with acquired HO experienced a treatment-related AE of vomiting, which was mild in intensity but resulted in a temporary dose reduction of study medication
  - A 17-year-old patient with acquired HO experienced a serious AE (*Clostridium difficile*) considered not related to setmelanotide, for which she was hospitalized; this caused disruption of the per-protocol dose escalation (Weeks 2 to 4), and the patient had nausea and vomiting throughout the study, completing the Week-16 visit on Day 113

Conclusions

- In this cross-sectional analysis, regardless of age, pediatric patients with obesity related to POMC or LEPR deficiencies, BBS, and acquired HO achieved clinically meaningful improvements in weight-related measures with no new safety signals
- The greater absolute reduction in BMI Z score among those ages 2-5 years across obesity causes may reflect overall higher baseline scores and highlights the importance of early intervention
  - Conversely, development-related body composition changes may affect BMI measurement across age subgroups
- The safety profile of setmelanotide was consistent across age groups and obesity cause
- More work is needed to understand the variation in response across obesity cause and analyze the impact beyond changes in weight-related measures alone (eg, body composition, hyperphagia, and quality of life)

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