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

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Summary

- **Treatment with setmelanotide resulted in clinically meaningful reductions in weight-related parameters with a consistent safety profile across pediatric and adolescent patients with genetic or acquired diseases of obesity that affect melanocortin-4 receptor (MC4R) signaling**

Introduction

- Under physiologic conditions, the hypothalamic MC4R pathway regulates hunger, satiety, energy expenditure, and, consequently, body weight[1-4]
- Disruptions in this pathway are associated with hyperphagia and early-onset, severe obesity[2-6]
  - This includes patients with proopiomelanocortin (POMC) deficiency, leptin receptor (LEPR) deficiency, Bardet-Biedl syndrome (BBS), and acquired hypothalamic obesity (HO)
- The MC4R agonist setmelanotide reduced body mass index (BMI) and hunger in clinical trials of pediatric patients in these populations and was well tolerated[6-8]
- 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 parameters after 12 months of setmelanotide in patients stratified by age groups of 6-11 and 12-17 years

Methods

- Patients aged 6-17 years were enrolled in 4 clinical trials of setmelanotide
  - Included in this analysis were patients from Phase 3 studies with POMC (including variants in *PCSK1*) deficiency (NCT02896192), LEPR deficiency (NCT03287960), or BBS (NCT03746522), and patients with HO from a Phase 2 study (NCT04725240) who entered a long-term extension trial (NCT03651765) and completed 12 months of setmelanotide treatment
- Changes in BMI Z score (Centers for Disease Control and Prevention calculation) and percent of the 95th BMI percentile (%BMI95) from index trial baseline after 12 months of setmelanotide were assessed
- Safety was evaluated by AE frequency

Results

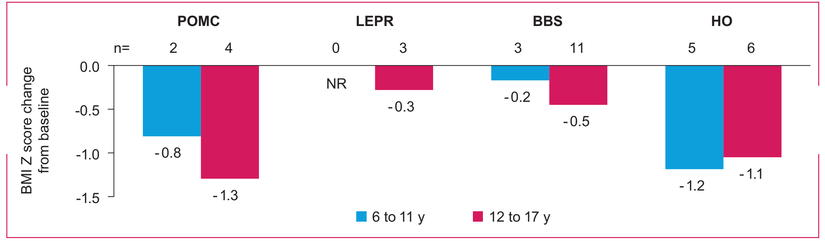
Patient disposition and baseline characteristics

- A total of 38 pediatric patients were included in the analysis at baseline including those with deficiencies of POMC (n=6) or LEPR (n=3), BBS (n=16), and HO (n=13; Table 1)
  - 2 patients with BBS and 2 patients with acquired HO had not received 52 weeks of setmelanotide treatment; therefore, their measurements were not included in Week-52 calculations
- After dose titration, patients received a mean (standard deviation) maximum dose of 1.6 (0.2) mg (POMC deficiency), 2.2 (0.6) mg (LEPR deficiency), 3.0 (0.0) mg (BBS), or 2.5 (0.7) mg (HO)

Efficacy outcomes

- The mean BMI Z score was reduced in those with deficiencies of POMC (ages 6-11 y: 0.8; 12-17 y: 1.3) or LEPR (6-11 y: not reported; 2-17 y: 0.3), BBS (6-11 y: 0.2; 12-17 y: 0.5), and HO (6-11 y: 1.2; 12-17 y: 1.1) (Figure 1)

Figure 1. 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.

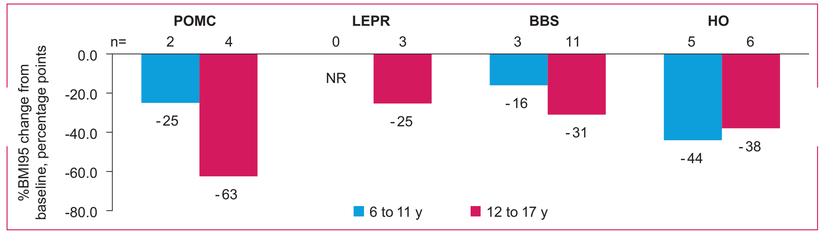
Table 1. Patient Baseline Characteristics

	POMC		LEPR		BBS		HO	
	6-11 y	12-17 y	6-11 y	12-17 y	6-11 y	12-17 y	6-11 y	12-17 y
n	2	4	0	3	3	13	5	8
Sex, n								
Female	1	2	—	2	2	6	2	2
Male	1	2	—	1	1	7	3	6
Race, n								
White	1	3	—	3	3	11	4	8
Black	—	—	—	—	—	1	1	—
Other*	1	1	—	—	—	1	—	—
Hispanic or Latinx, n								
Yes	1	—	—	—	—	—	2	1
No	1	4	—	3	3	13	3	7
Weight, mean (SD), kg	63.9 (8.0)	122.7 (12.9)	—	108.5 (13.6)	83.3 (24.5)	101.4 (27.7)	70.6 (22.1)	111.9 (21.7)
BMI Z score, mean (SD)	2.12 (0.05)	2.63 (0.12)	—	2.57 (0.20)	2.79 (0.06)	2.49 (0.38)	2.69 (0.18)	2.46 (0.25)
%BMI95 (SD), percentage points	117 (2)	154 (13)	—	152 (19)	170 (19)	157 (48)	157 (23)	138 (15)
Waist circumference, mean (SD), cm	95.0 (9.0)	121.5 (6.0)	—	110.0 (4.3)	100.6 (15.0)	108.1 (17.7)	97.1 (15.1)	118.1 (9.9)

*Other includes Arabic, Moroccan, Middle Eastern, or native Hawaiian or other Pacific Islander. BBS, Bardet-Biedl syndrome; BMI, body mass index; HO, hypothalamic obesity; LEPR, leptin receptor deficiency; POMC, proopiomelanocortin deficiency; SD, standard deviation.

- The mean %BMI95 was reduced in patients with deficiencies of POMC (ages 6-11 y: 25; 12-17 y: 63) or LEPR (6-11 y: not reported; 12-17 y: 25), BBS (6-11 y: 16; 12-17 y: 31), and HO (6-11 y: 44; 12-17 y: 38) (Figure 2)

Figure 2. Mean %BMI95 reduction at 52 weeks.



%BMI95, percent of the 95th body mass index percentile; BBS, Bardet-Biedl syndrome; HO, hypothalamic obesity; LEPR, leptin receptor deficiency; NR, not reported; POMC, proopiomelanocortin deficiency.

Safety outcomes

- All 38 patients had AEs of any causality during the 52-week period (Table 2)
- The most frequent AEs overall were skin hyperpigmentation (n/N=27/38; 71%), injection site erythema (n/N=20/38; 53%), and nausea (n/N=19/38; 50%)
- AE frequency and severity did not appear to meaningfully differ by age group
- Serious AEs or treatment-related AEs leading to study discontinuation during the 52 weeks occurred in 2 patients (1 HO; 1 BBS)
  - A 17-year-old patient with HO experienced a serious AE (*Clostridioides difficile* colitis) considered not related to setmelanotide for which she was hospitalized but caused disruption of the per-protocol dose escalation (Weeks 2 to 4); the patient had nausea and vomiting throughout the study and completed the Week-16 visit on Day 113 but did not continue into the long-term extension study
  - A 12-year-old patient with BBS experienced treatment-related AEs of nausea and vomiting that were moderate in intensity and led to treatment discontinuation on Day 124

Table 2. Number of Adverse Events

	All	POMC		LEPR		BBS		HO	
	6-17 y	6-11 y	12-17 y	6-11 y	12-17 y	6-11 y	12-17 y	6-11 y	12-17 y
Any AE	**38 (100%)**	**2**	**4**	**—**	**3**	**3**	**13**	**5**	**8**
Related to study drug	36 (95%)	2	4	—	3	3	13	3	8
Dose interruption or decrease	10 (26%)	1	0	—	0	1	2	2	4
Treatment-related AE leading to discontinuation	1 (3%)	0	0	—	0	0	1	0	0
Serious treatment-related AE	0	0	0	—	0	0	0	0	0
AE resulting in death	0	0	0	—	0	0	0	0	0
Patients experiencing AEs ≥15% in all patients, any causality									
Skin hyperpigmentation	26 (68%)	2	4	—	2	2	10	1	5
Injection site erythema	20 (53%)	2	4	—	3	2	8	0	1
Nausea	17 (45%)	1	4	—	1	1	3	2	5
Vomiting	15 (39%)	0	4	—	0	2	5	1	3
Injection site pruritus	13 (34%)	2	2	—	1	1	5	0	2
Injection site pain	12 (32%)	0	1	—	1	2	5	1	2
Headache	10 (26%)	0	2	—	1	1	3	1	2
Injection site edema	10 (26%)	1	4	—	2	1	2	0	0
Diarrhea	9 (24%)	0	3	—	0	1	2	0	3
Upper respiratory tract infection	9 (24%)	1	4	—	0	0	1	2	2
Injection site bruising	9 (24%)	2	0	—	2	2	3	0	0
Injection site induration	8 (21%)	0	0	—	2	2	2	1	1
Back pain	7 (18%)	0	2	—	1	0	1	2	1
Abdominal pain	7 (18%)	0	3	—	0	0	1	1	2
Spontaneous erections	5 (24%)*	0	0	—	0	0	1	0	4
Patients experiencing AEs of special interest <15%									
Depression/major depression	1 (3%)	1	0	—	0	0	0	0	0
Suicidal ideation	2 (5%)	1	0	—	0	0	0	0	1
Melanocytic nevus	5 (13%)	1	1	—	0	0	3	0	0

*Male patients only (n=21). AE, adverse event; BBS, Bardet-Biedl syndrome; HO, hypothalamic obesity; LEPR, leptin receptor deficiency; NR, not reported; POMC, proopiomelanocortin deficiency.

Conclusions

- Pediatric patients with obesity related to deficiencies of POMC or LEPR, BBS, or HO achieved clinically meaningful improvements in weight-related parameters regardless of age group
- More work is needed to understand the variation in response across obesity causes and analyze the impact beyond changes in weight-related parameters alone (eg, hyperphagia and quality of life)
- These findings support the use of setmelanotide in children aged 6-17 years in hypothalamic MC4R pathway disruptions

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