Clinical Characteristics of 2 to 5-Year-Old Patients With Hyperphagia and Obesity Secondary to Melanocortin-4 Receptor Pathway Diseases and 1-Year Response to Setmelanotide

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Introduction

- The hypothalamic melanocortin-4 receptor (MC4R) pathway regulates energy balance and food intake[1-4]
- Impaired MC4R pathway signaling in patients with Bardet-Biedl syndrome (BBS), proopiomelanocortin (POMC) deficiency, or leptin receptor (LEPR) deficiency can cause hyperphagia and early-onset, severe obesity[1-5]
  - Hyperphagia is a chronic pathologic condition characterized by insatiable hunger, impaired satiety, and abnormal food-seeking behaviors[6]
- In the United States, setmelanotide is an MC4R agonist that is approved to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to BBS or POMC (including variants in *PCSK1*) or LEPR deficiency[7]
  - In a pivotal Phase 3 multicenter open-label trial in patients aged 2-5 years with BBS, POMC deficiency, or LEPR deficiency, setmelanotide treatment led to clinically meaningful reductions in age-appropriate weight measures at 1 year[8]
- Response to setmelanotide may vary owing to differences in age, obesity severity, pathophysiology, and underlying disease states or because of the variable mechanism of MC4R pathway dysfunction

Objective

- To report weight class changes from a pivotal Phase 3, open-label trial in patients with BBS, POMC deficiency, or LEPR deficiency aged 2-5 years after 1 year of setmelanotide treatment

Methods

Trial Design

- Patients aged 2-5 years with hyperphagia and obesity with genetically confirmed BBS, biallelic *POMC* or *PCSK1* variants (POMC deficiency), or biallelic *LEPR* variants (LEPR deficiency) were eligible
- Patients with documented adherence of >75% to setmelanotide treatment through 1 year were included in this post hoc analysis
- 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

Outcomes

- Changes in percent of the body mass index (BMI) 95th percentile (%BMI95) from index trial baseline to 1 year of setmelanotide were assessed and stratified by weight categories (healthy weight [≥5th to <85th BMI percentile], overweight [≥85th to <95th BMI percentile], class I obesity [%BMI95 ≥95% to <120%], class II severe obesity [%BMI95 ≥120% to <140%], or class III extreme obesity [%BMI95 ≥140%])
- Changes in BMI Z score (Centers for Disease Control and Prevention [CDC] and World Health Organization [WHO] methodologies) at 1 year were also assessed

Results

Patient Disposition and Baseline Characteristics

- Ten of 12 patients who were enrolled completed the trial on continuous treatment and were included in the analysis (BBS, n=4; POMC, n=3; LEPR, n=3; Table)
- Overall, 9 of 10 patients had class II (severe) obesity or greater at baseline and 25% (1/4), 100% (3/3), and 100% (3/3) had class III (extreme) obesity in the BBS, POMC, and LEPR cohorts at baseline, respectively

Table. Patient Demographics and Characteristics

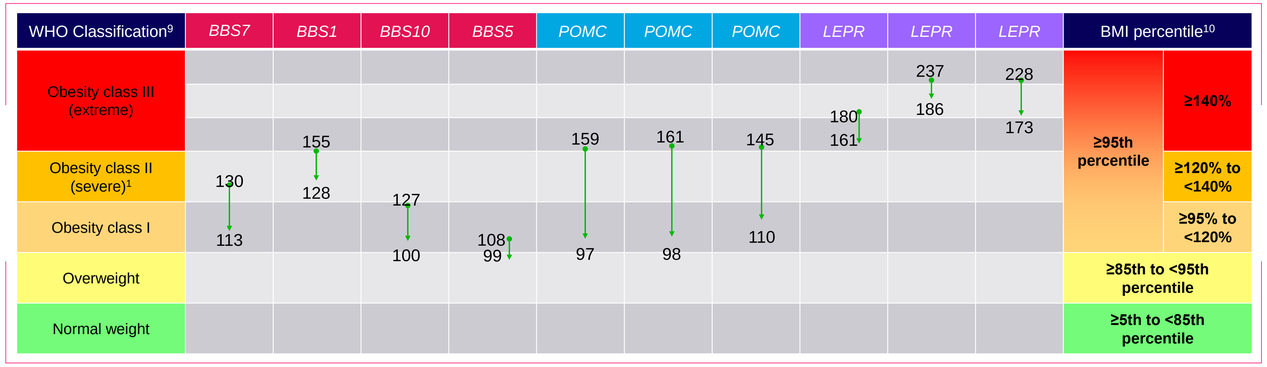
	BBS	POMC deficiency	LEPR deficiency	Total
Enrolled patients, n	5	3	4	12
Age, mean (SD [range]), y	3.8 (1.3 [2-5])	3.3 (0.6 [3-4])	3.5 (0.6 [3-4])	3.6 (0.9 [2-5])
Male, n (%)	2 (40)	3 (100.0)	2 (50.0)	7 (58.3)
Race, n (%)				
White	4 (80.0)	-	3 (75.0)	7 (58.3)
Asian	1 (20.0)	-	-	1 (8.3)
Other	-	1 (33.3)	1 (25.0)	2 (16.7)
Not reported/unknown	-	2 (66.6)	-	2 (16.7)
Ethnicity, n (%)				
Hispanic or Latino	-	-	1 (25.0)	1 (8.3)
Not Hispanic or Latino	5 (100)	1 (33.3)	3 (75.0)	9 (75.0)
Not reported/unknown	-	2 (66.6)	-	2 (16.7)
BMI, mean (SD), kg/m^2	23.7 (3.5)	27.8 (1.6)	39.3 (4.8)	29.9 (7.9)
BMI Z score, mean (SD)				
CDC	3.1 (0.7)	4.8 (0.7)	4.9 (1.6)	4.2 (1.4)
WHO	4.2 (1.1)	7.5 (0.8)	13.2 (3.3)	8.0 (4.4)
%BMI95, mean (SD)	128.8 (16.7)	155.1 (8.5)	218.1 (25.8)	165.1 (44.1)

BBS, Bardet-Biedl syndrome; BMI, body mass index; CDC, Centers for Disease Control and Prevention; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation; WHO, World Health Organization.

Changes in Weight Category

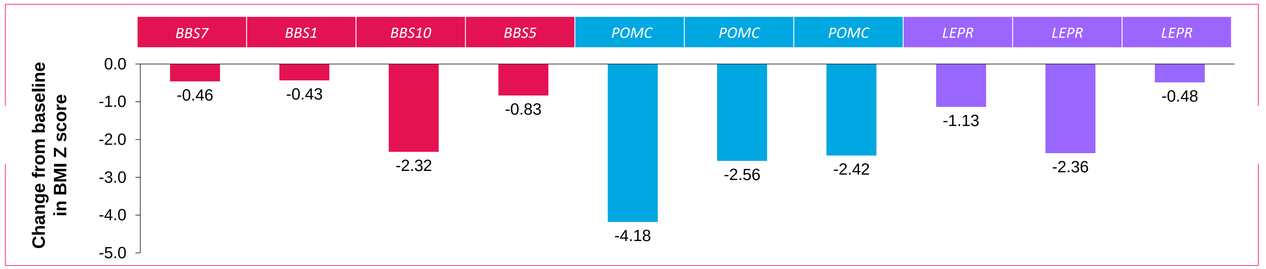
- After 1 year, improvements in ≥1 obesity class were observed in 3 of 4 patients with BBS (75%; variants in *BBS1*, *BBS7*, and *BBS10* [n=1 each]) and 3 of 3 patients in the POMC cohort (100%; Figure 1)
- The LEPR cohort did not show any improvements in obesity class, although they started at higher baseline BMI, and marked within-category reductions in BMI were observed (mean [SD] reductions in %BMI95 of 45 [20] percentage points, CDC BMI Z score of 1.32 [1.00], or WHO BMI Z score of 4.82 [2.49])
- The change from baseline in BMI Z score ranged from −0.46 to −4.18 (Figure 2)

Figure 1. On-Treatment Change in %BMI95 (WHO) Weight Category (n=10) at Year 1 in Patients With BBS, POMC Deficiency, or LEPR Deficiency



%BMI95, percent of the 95th BMI percentile; BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; WHO, World Health Organization.

Figure 2. Change in BMI Z Score at Year 1 in Patients With BBS, POMC Deficiency, or LEPR Deficiency



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

Safety Concerns

- There were no deaths, serious adverse events (AEs), or AEs leading to drug discontinuation
- There was no evidence of impaired growth or neurocognitive development
- The most common AEs (occurring in ≥25% of patients) were skin hyperpigmentation (9/12 [75%]); vomiting (7/12 [58%]); nasopharyngitis (5/12 [42%]); upper respiratory tract infection, injection site bruising, injection site pruritus, pyrexia, fall, and melanocytic naevus (6/12 [50%] each); and injection site discoloration and cough (3/12 [25%] each)

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Writing and editorial support for this poster were provided under the direction of the authors by MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

Disclosures: All authors' institutions received research funding from Rhythm Pharmaceuticals, Inc. JA and ISF have received compensation for advisory board participation, consulting, and/or lectures; JA is a BBS Advisory Board member. CC, CS, GY, and JCG are employees and receive stock options from Rhythm Pharmaceuticals, Inc.

Conclusions

- In distinct pediatric populations aged 2-5 years with obesity who remained on treatment for 52 weeks, setmelanotide generally reduced body weight and improved weight category, albeit with differing intensity, potentially due to the variable mechanisms and location of MC4R pathway dysfunction
- No serious AEs or AEs leading to study discontinuation were observed
  - Common AEs were similar to those observed in previous trials
- These data further highlight the impact early intervention with targeted therapy can have in reducing weight in pediatric patients with obesity due to BBS, POMC deficiency, or LEPR deficiency

References: 1. Baldini G, Phelan KD. *J Endocrinol*. 2019;241:R1-R33. **2.** Farooqi IS, O'Rahilly S. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **3.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **4.** van der Klaauw, Farooqi. *Cell*. 2015;161:119-132. **5.** Seo et al. *Hum Mol Genet*. 2009;18:1323-1331. **6.** Heymsfield et al. *Curr Obes Rep*. 2025;14:13. **7.** IMCIVREE [package insert]. Boston, MA; Rhythm Pharmaceuticals, Inc.; 2024. **8.** Argente et al. *Lancet Diabetes Endocriol*. 2025;13:29-37. **9.** [No authors listed]. *Obes Res*. 1998;6(suppl 2):51S-209S. **10.** Hampl et al. *Pediatrics*. 2023;151:e2022060640.