RESTORE: Baseline Findings From a Real-world Study of Setmelanotide in Patients With Rare Melanocortin-4 Receptor Pathway Diseases

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Introduction

- The melanocortin-4 receptor (MC4R) pathway in the hypothalamus regulates hunger, satiety, and energy expenditure[1-2]
- Genetic variants and/or injury to the hypothalamus can result in rare MC4R pathway diseases, which are characterized by obesity and hyperphagia (pathological, insatiable hunger)[2-3]
- Setmelanotide, an MC4R agonist, is approved for reducing excess body weight and maintaining weight reduction long-term in patients aged ≥2 years with obesity due to rare MC4R pathway diseases including Bardet-Biedl syndrome (BBS) and proopiomelanocortin (POMC; including biallelic variants in *PCSK1*) deficiency or leptin receptor (LEPR) deficiency[4]
- RESTORE is an ongoing prospective, observational, longitudinal study assessing the real-world effectiveness of setmelanotide in patients with BBS or POMC/LEPR deficiency in US clinical settings.

Objective

- To describe patient baseline characteristics and clinical burden associated with BBS in a real-world setting, before setmelanotide initiation

Methods

Study Population

- Patients aged ≥6 years and caregivers aged ≥18 years in the United States who consented into the Rhythm InTune Patient Support Program and not yet initiated treatment with setmelanotide

Data Collection

- Patients complete secure online surveys at baseline (ie, before setmelanotide initiation) and at post-treatment initiation time points over a 1-year period
  - Caregivers complete surveys for patients aged <12 years and those who cannot self-report

Outcomes

- Patient demographics including sociodemographic characteristics, clinical characteristics, and use of weight management programs and treatments were collected
- Key outcomes evaluated included hyperphagia-related signs and symptoms (ie, Symptoms of Hyperphagia [SoH], Impacts of Hyperphagia [IoH]), global hunger assessment, global health status, and level of physical activity

Statistical Analysis

- Descriptive analysis was conducted for baseline characteristics and clinical burden associated with BBS
- Selected characteristics and burden were summarized by age group (ie, pediatric patients aged 6-17 years and adult patients)

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References: 1. Ayers et al. *J Clin Endocrinol Metab.* 2018;103:2601-2612. **2.** Huvenne et al. *Obes Facts.* 2016;9:158-173. **3.** Rose et al. *Obesity.* 2018;26:1727-1732 **4.**IMCIVREE (setmelanotide) [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; 2024. **5.** *World Health Organ Tech Rep Ser.* 2000;894:i-xii **6.** Freedman et al. *Pediatrics.* 2017; 140(3):e2017072

Results

Patient Baseline Characteristics

- By April 2025, a total of 64 patients with BBS had enrolled in the study, including 44 adults and 20 pediatric patients (**Table 1**)
- The mean age (SD) of patients at enrollment was 30.8 (16.1); most were female (71.9%) and white (87.5%) (**Table 1**)

Medical History and Conditions

- The mean baseline BMI for adult patients (47.9) corresponded with severe Class 3 obesity; the mean pediatric BMI z-score (4.7) also corresponded with severe obesity.[5-6]
- Hyperphagia was the most common symptom of BBS (81.3%), followed by ataxia (50.0%) and developmental delay (46.9%) (**Table 1**)
  - Among patients with hyperphagia (n=52), 86.5% reported that their hunger contributed to their BBS diagnosis
- Anxiety and depression (67.2%), seasonal allergies (50.0%), and sleep apnea (46.9%) were the most common comorbidities (**Table 1**)

Table 1. Baseline Patient Characteristics

	Overall N=64
Sociodemographics	
Sex at birth, n (%)	
Male	18 (28.1)
Female	46 (71.9)
Race,* n (%)	
White	56 (87.5)
Black or African American	3 (4.7)
Asian	3 (4.7)
American Indian or Alaska Native	2 (3.1)
Native Hawaiian or Other Pacific Islander	1 (1.6)
Other	1 (1.6)
Ethnicity, n (%)	
Hispanic/Latino or of Spanish origin	5 (7.8)
Not Hispanic/Latino	59 (92.2)
Health insurance,* n (%)	
Commercial or private insurance	38 (59.4)
Medicaid	25 (39.1)
Medicare	8 (12.5)
Other type of insurance	5 (7.8)
Medical history and conditions	
Age at BBS symptom onset, mean (SD; median)	4.0 (3.5; 4.3)
Genetic test performed as part of diagnosis, n (%)	
Yes	62 (96.9)
No	2 (3.1)
Top 5 BBS-related manifestations*	
Hyperphagia	52 (81.3)
Ataxia or poor coordination	32 (50.0)
Developmental delay	30 (46.9)
Rod-cone dystrophy	28 (43.8)
Speech delay	20 (31.3)
Common comorbidities,* n (%)	
Anxiety/Depression	43 (67.2)
Seasonal allergies	32 (50.0)
Sleep apnea	30 (46.9)
Hypertension	22 (34.4)
Eczema	19 (29.7)
Age-group–specific characteristics	
Pediatric (≥6 and <18 y), n (%)	20 (31.2)
Age, mean (SD; median), y	11.6 (3.6; 11.5)
Weight, mean (SD; median), lbs	211.7 (79.2; 203.5)
Modified BMI Z score, mean (SD; median)	4.7 (2.6; 4.4)
Age at BBS diagnosis, mean (SD; median), y	10.7 (4.5; 11.3)
Adult (≥18 years), n (%)	44 (68.8)
Age, mean (SD; median)	39.6 (11.0; 38.0)
Weight, mean (SD; median), lbs	309.1 (76.4; 294.5)
BMI, mean (SD; median), kg/m^2	47.9 (9.4; 47.7)
Age at BBS diagnosis, mean (SD; median), y	38.3 (14.0; 37.6)

*Values may not add up to 100% as patients may fall under more than one category. Of the 64 patients, 43 adults and 4 children were able to self-report
BBS, Bardet-Biedl syndrome; BMI, Body mass index; SD, Standard deviation.

Table 2. Weight Management Approaches, Medications, and Surgery

	Overall N=64
Nonmedication weight management approaches and medications	
Current number of nonmedication approaches,* mean (SD; median)	6.5 (3.3; 6.5)
Number of patients using any medication,† n (%)	30 (46.9)
Effectiveness of nonmedication weight management approaches/ medications, n (%)	
Lost some weight and did not regain it	6 (9.4)
Lost some weight but partially regained it	8 (12.5)
Lost some weight but fully regained it	28 (43.8)
Did not lose weight	7 (10.9)
Continued to gain weight	15 (23.4)
Surgery	
Received weight loss (bariatric) surgery, n (%)	15 (23.4)
Effectiveness of weight loss (bariatric) surgery, n (%)	
Lost some weight and did not regain it	1 (6.7)
Lost some weight but partially regained it	7 (46.7)
Lost some weight but fully regained it	7 (46.7)

*A total of 14 nonmedication weight management approaches were included in the survey: drink more water, limit how much or how often eating certain foods, make sure to have enough sleep, plan healthy meals, eat smaller portion sizes, increase time spent exercising or start exercising, measure weight regularly, avoid or reduce sugar intake, count or restrict carbohydrate intake, count or restrict calories, limit screen time and/or sedentary time, count or restrict fat intake, engage in fasting, lock up food at night. †A total of 10 medications were included in the survey: metformin, Mounjaro (tirzepatide), Qsymia (phentermine/topiramate), Ozempic (semaglutide), Wegovy (semaglutide), Saxenda (liraglutide), Contrave (naltrexone/bupropion), Xenical/Alli (orlistat), Zonegran (zonisamide), and Trulicity (dulaglutide).
SD, standard deviation.

Weight Management Approaches

- Almost half reported using ≥1 weight management medication, and nearly one-fourth of patients received bariatric surgery (**Table 2**)
- Approximately 80% of patients failed to lose weight by weight management approaches and medications; Nearly 50% of patients failed to lose weight by bariatric surgery (**Table 2**)

Symptoms and Impacts of Hyperphagia

- Among patients with hyperphagia (n=52), hyperphagic behaviors presented throughout the day at baseline (**Figure 1**)
  - All patients who could self-report felt hungry right after eating; 75% hid food from others ≥1 time during the day
  - Nearly all patients not able to self-report (93%) negotiated for food and asked for more food right after eating ≥1 time per day; >80% ate extremely fast
- Hyperphagia had a negative impact on most patients across domains, including mood/emotion, work/school, and leisure/recreational activities (**Figure 1**)
  - For self-reporting patients, the greatest impacts were on mood/emotions and leisure or recreational activities
  - Among patients who cannot self-report, work/school and leisure or recreational activities were most impacted

Table 3. Symptoms of Hyperphagia and Impacts of Hyperphagia Composite Scores*

	Self-report n=37
SoH score (range, 0-2), mean (SD; median)	0.9 (0.4; 1.0)
IoH score (range, 0-3), mean (SD; median)	1.5 (0.7; 1.5)
	Caregiver report n=15
SoH score (range, 0-2), mean (SD; median)	1.2 (0.4; 1.2)
IoH score (range, 0-3), mean (SD; median)	1.8 (0.7; 1.6)

*SoH and IoH were collected exclusively from individuals who reported having hyperphagia (n=52). Higher scores for the SoH and IoH indicate more severe hyperphagia and impacts of hyperphagia, respectively. The recall period of SoH is the past 24 hours; the recall period of IoH is the past 7 days. IoH, Impact of Hyperphagia; SD, standard deviation; SoH, Symptoms of Hyperphagia.

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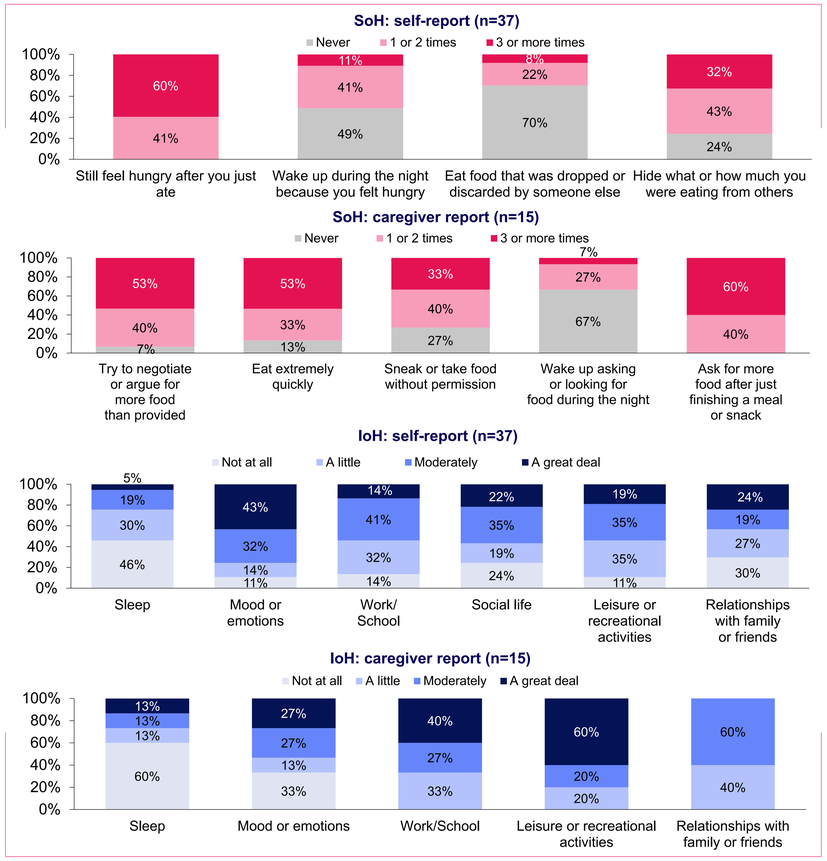
Figure 1. Symptoms of Hyperphagia and Impacts of Hyperphagia Item-Level Responses



Health Status

- Most patients (67.2%) reported being sedentary or lightly active (**Figure 2**)
- Across all patients, approximately 60% were in poor or fair health (**Figure 3**)

Figure 2. Baseline Level of Physical Activity

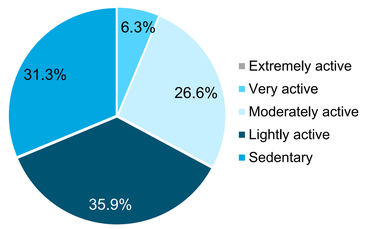
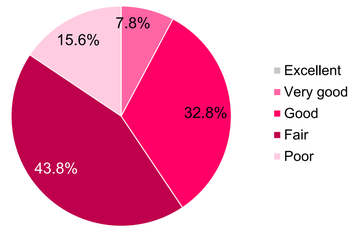


Figure 3. Global Health Status



The recall period of global health status is in the past 4 weeks.

Conclusions

- Baseline data from the RESTORE study provide deeper insights into the substantial clinical burden in patients with BBS prescribed setmelanotide
- Hyperphagia is highly prevalent (>80%) and has broad, multi-faceted impacts on patients' lives, extending beyond physical health to emotional well-being, school/work, and leisure
- Patients also experience substantial weight management burden, with pharmacological and non-pharmacological approaches providing limited short- or long-term effectiveness
- Findings from follow-up surveys will longitudinally assess the clinical and health-related quality of life impacts of setmelanotide use in this patient population