# Effect of Setmelanotide on Weight Category in Patients With BBS and Obesity

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## Introduction

- The melanocortin-4 receptor (MC4R) pathway in the brain regulates hunger, satiety, and weight[1]
- In patients with the ciliopathy Bardet-Biedl syndrome (BBS), MC4R activation is reduced because of impaired leptin receptor signaling, which can lead to hyperphagia (pathologic, insatiable hunger) and severe obesity[2-4]
- The MC4R agonist setmelanotide has demonstrated clinically meaningful weight and hunger reductions in patients with obesity due to BBS[5,6]

## Objectives

- To report weight trajectories of patients with BBS stratified by weight and changes in self-reported or caregiver-reported hunger after 1 year of setmelanotide treatment

## Methods

- Patients with BBS aged ≥2 years from 2 pivotal clinical trials of setmelanotide (NCT03746522 and NCT04966741) who had data at baseline and 1 year were included in this post hoc analysis
- Changes in body mass index (BMI; for adult patients age ≥18 years) and percent of the 95th BMI percentile (%BMI95; for pediatric patients age <18 years) from index trial baseline to 1 year were assessed and stratified by weight categories (stratification by BMI in patients age ≥18 years: healthy weight [BMI ≥18.5 to <25 kg/m$^2$], overweight [BMI ≥25 to <30 kg/m$^2$], class I obesity [BMI ≥30 to <35 kg/m$^2$], class II severe obesity [BMI ≥35 to <40 kg/m$^2$], or class III extreme obesity [BMI ≥40 kg/m$^2$]; stratification by %BMI95 in patients age <18 years: healthy weight [≥5th to <85th percentile], overweight [≥85th to <95th percentile], class I obesity [%BMI95 ≥95% to <120% or BMI ≥30 to <35 kg/m$^2$, whichever was lower], class II severe obesity [%BMI95 ≥120% to <140% or BMI ≥35 to <40 kg/m$^2$, whichever was lower], or class III extreme obesity [%BMI95 ≥140% or BMI ≥40 kg/m$^2$, whichever was lower])
  - For pediatric patients at a BMI percentile of ≥95%, data are reported as %BMI95; for pediatric patients at a BMI percentile <95%, data are reported as BMI percentile
- The change from baseline in BMI Z score was also assessed in pediatric patients
- Hunger assessments were selected based on the specific study patients were enrolled in, their age, and their ability to self-report
  - For patients enrolled in NCT04966741 (all of whom were 2-<6 years old): the Caregiver-Reported Global Hunger Questions (Caregiver Global Impression of Change item) were used; caregivers were asked, "How hungry has your child acted in the past 7 days compared to before starting this study?" with response options ranging from "much less hungry" to "much more hungry"
  - For patients enrolled in NCT03746522:
    - In adult and pediatric patients (≥6 years old) who could not self-report, the caregiver-reported Prader-Willi Syndrome Food Problem Diary (PWS-FPD) was used. This 10-item questionnaire assesses the frequency of behaviors that are commonly exhibited more than once in a 24-hour period, as well as less common behaviors that may be indicative of more severe food-seeking behaviors; scores range from 0 to 30, with higher scores suggesting more severe hyperphagia/food-seeking behaviors
    - In adult and pediatric patients (≥12 years old) who were able to self-report, hunger was assessed using the Hunger Questions for Patients ≥12 Years of Age. This questionnaire includes 3 items (average, most, and morning hunger) that are designed to be evaluated separately; this analysis assessed the "most" hunger score. Patients were asked, "In the last 24 hours, how hungry did you feel when you were the most hungry?" and could respond from "not hungry at all" for a score of 0 up to "hungriest possible" for a score of 10
    - In 2 pediatric patients aged 6-<12 years, hunger was assessed using Hunger Questions for Patients 6 to <12 Years of Age, which is a pictorial (smiley face visual analog scale) version of a Likert rating scale; patients were asked, "How hungry do you feel right now" and could reply "not hungry at all" for a score of 0 up to "hungriest possible" for a score of 4

## Results

### Patient Disposition and Baseline Characteristics

- Overall, 31 patients with BBS were analyzed (Table 1)
  - Most patients (67.7%) had class III severe obesity at baseline

**Table 1.** Demographics and Baseline Characteristics

| | Age <18 y (n=19) | Age ≥18 y (n=12) | Total (N=31) |
|---|---|---|---|
| Age, n (%) | | | |
| <18 y | 19 (100) | - | 19 (61.3) |
| ≥18 y | - | 12 (100) | 12 (38.7) |
| Sex, n (%) | | | |
| Female | 11 (57.9) | 7 (58.3) | 18 (58.1) |
| Male | 8 (42.1) | 5 (41.7) | 13 (41.9) |
| Race, n (%) | | | |
| White | 17 (89.5) | 10 (83.3) | 27 (87.1) |
| Black or African American | 1 (5.3) | 0 | 1 (3.3) |
| Asian | 1 (5.3) | 0 | 1 (3.3) |
| Other* | 0 | 2 (16.7) | 2 (6.7) |
| Ethnicity, n (%) | | | |
| Not Hispanic or Latino | 19 (100) | 11 (91.7) | 30 (96.8) |
| Hispanic or Latino | 0 | 1 (8.3) | 1 (3.3) |
| Other or unknown | 0 | 0 | 0 |
| %BMI95, mean (SD) | | | |
| <18 y | 151.8 (44.6) | - | 151.8 (44.6) |
| BMI, mean (SD), kg/m$^2$ | | | |
| ≥18 y | - | 47.9 (6.1) | 47.9 (6.1) |
| Hunger assessments, mean (SD)† | | | |
| PWS-FPD‡ | 8.3 (9.2); n=7 | 1.9 (1.6); n=4 | 6.0 (7.9); n=11 |
| Daily most hunger | 6.0 (1.0); n=3 | 7.1 (1.3); n=7 | 6.8 (1.3); n=10 |
| VAS of self-reported hunger | 2.0 (0.0); n=2 | - | 2.0 (0.0); n=2 |

*Includes those of mixed race. †Baseline assessments were not performed for the Caregiver-Reported Change in Global Hunger Questionnaire. ‡Caregiver-reported. %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; PWS-FPD, Prader-Willi Syndrome Food Problem Diary; VAS, visual analog scale.

### Changes in Weight Category

- After 1 year, 14 patients had an improvement of ≥1 weight category (45.2%), of whom 2 improved 2 categories
- Two patients (6.4%) improved from obesity/overweight to healthy weight
- Clinically meaningful reductions in BMI were observed in adult patients (range, −8.3% to −9.5%) and in BMI Z score in all pediatric patients (range, −0.16 to −2.32) and in patients aged 2-<6 years (range, −0.16 to −2.32)
- Overall, 28 patients (90.3%) experienced improvements in BMI (Figure 1) or %BMI95 (Figure 2)

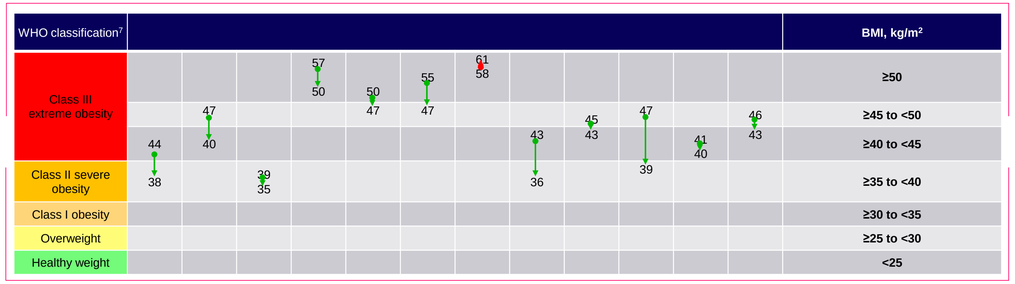
### Hunger Assessment

- Of 28 patients with available hunger data, 25 (89.3%) had reduced hunger (Table 2)
  - One patient ≥18 years maintained a score of 6 on the daily most hunger questionnaire, 1 patient <18 years was reported as being "much more hungry" on the Caregiver-Reported Change in Global Hunger, and 1 patient <18 years scored 0.3 on the PWS-FPD at baseline and 0.7 at Week 52 (30-point scale)

### Safety Outcomes

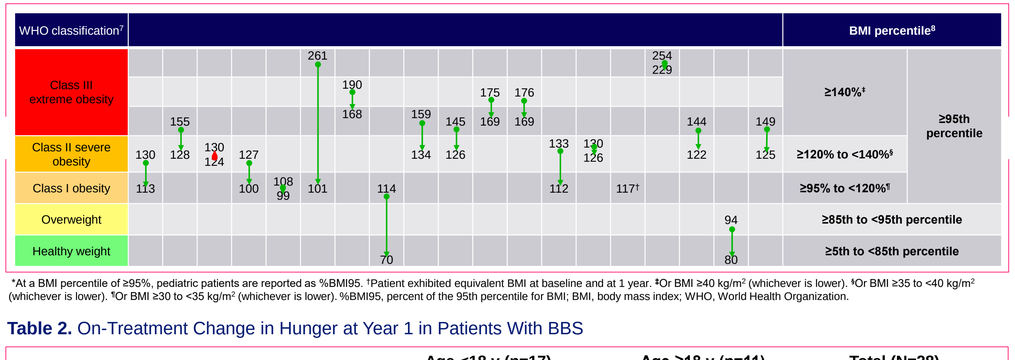
- Setmelanotide was well tolerated; common adverse events across cohorts included skin hyperpigmentation, nausea, and vomiting[5,6]

**Figure 1.** On-Treatment Change in Weight Category at Year 1 in Adult Patients With BBS (≥18 Years Old)




BMI, body mass index; WHO, World Health Organization.

**Figure 2.** On-Treatment Change in Weight Category at Year 1 in Pediatric Patients With BBS (<18 Years Old*)




*At a BMI percentile of ≥95%, pediatric patients are reported as %BMI95. †Patient exhibited equivalent BMI at baseline and at 1 year. ‡Or BMI ≥40 kg/m$^2$ (whichever is lower). §Or BMI ≥35 to <40 kg/m$^2$ (whichever is lower). ¶Or BMI ≥30 to <35 kg/m$^2$ (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; WHO, World Health Organization.

**Table 2.** On-Treatment Change in Hunger at Year 1 in Patients With BBS

| | Age <18 y (n=17) | | Age ≥18 y (n=11) | | Total (N=28) | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| Caregiver-Reported Change in Global Hunger | | | | | | |
| Much more hungry | 1 | - | - | - | 1 | - |
| Somewhat less hungry | 2 | - | - | - | 2 | - |
| Much less hungry | 2 | - | - | - | 2 | - |
| PWS-FPD* | 7 | −6.3 (7.1) | 4 | −1.6 (1.7) | 11 | −4.6 (6.1) |
| Daily most hunger | 3 | −3.33 (2.1) | 7 | −2.9 (1.7) | 10 | −3.0 (1.7) |
| VAS of self-reported hunger† | 2 | −1.0 (0.0) | - | - | 2 | −1.0 (0.0) |

*Caregiver reported. †for patients 6-<12 years of age. PWS-FPD, Prader-Willi Syndrome Food Problem Diary; VAS, visual analog scale.

## Conclusions

- In adult and pediatric patients with obesity due to BBS, setmelanotide decreased BMI, improved weight category, and reduced hunger
- Improvements in weight category have been associated with improved quality of life and reduced comorbidity incidence
- The positive data in pediatric and adult patients presented herein add to the available evidence supporting use of setmelanotide as a targeted treatment in patients ≥2 years old with obesity due to BBS and support early intervention in pediatric patients

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**References: 1.** Krashes et al. *Nat Neurosci*. 2016;19:206-219. **2.** Guo et al. *PLoS Genet*. 2016;12:e1005890. **3.** Pomeroy et al. *Pediatr Obes*. 2021;16:e12703. **4.** Forsythe et al. *Orphanet J Rare Dis.* 2023;18:182. **5.** Argente et al. *Lancet Diabetes Endocrinol*. 2025;13:29-37. **6.** Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10:859-868. **7.** National Institutes of Health. *Obes Res*. 1998;6(suppl 2):51S-209S. **8.** Hampl et al. *Pediatrics*. 2023;151:e2022060640.