3-Year Setmelanotide Weight Outcomes in Patients With Bardet-Biedl Syndrome and Obesity

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416

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Summary

- **Setmelanotide demonstrated continued clinical benefit up to 3 years on weight-related outcomes in adults and pediatric patients with Bardet-Biedl syndrome (BBS)**

Introduction

- BBS is a rare syndromic form of obesity associated with renal abnormalities; rod-cone dystrophy; severe, early-onset obesity; and hyperphagia[1,2]
- BBS is caused by gene variants in 1 of ≥26 genes that can lead to cilia dysfunction and impairment of the melanocortin signaling pathway via impaired leptin receptor trafficking[2-5]
- Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, is indicated by the US Food and Drug Administration and the European Medicines Agency for chronic weight management in patients aged ≥6 years with specific forms of monogenic or syndromic obesity, including BBS[6]
  - In a pivotal Phase 3 trial, patients with BBS experienced meaningful reductions in weight-related measures and hunger scores following 52 weeks of setmelanotide treatment[2]
  - In a long-term follow-up study, up to 2 years of setmelanotide treatment was associated with sustained weight-related improvements in both pediatric and adult patients with BBS[7]

Objective

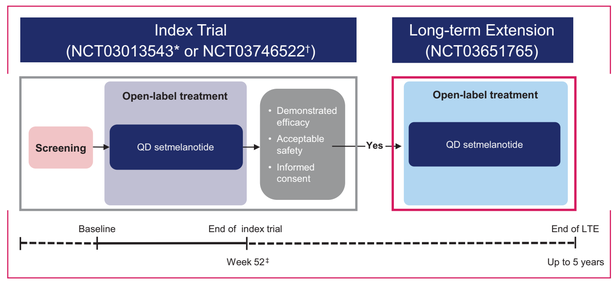
- To assess the long-term, on-treatment outcomes over ~3 years of setmelanotide therapy in patients with BBS

Methods

Trial design

- Patients aged ≥6 years were eligible for this long-term extension (LTE) trial (NCT03651765) if they
  - Completed a prior (index) trial in which they received setmelanotide
  - Demonstrated clinical benefit from treatment on the basis of efficacy results
- Patients with BBS enrolled in the LTE after completing a Phase 2 or 3 trial of setmelanotide[2,8]
  - Patients received ≥12 months of setmelanotide treatment as a part of their index trial
  - Patients were aged ≥6 years with obesity at the time of enrollment in the index trial
- Patients began the LTE immediately following completion of the index trial and continued on the same dose of setmelanotide (Figure 1)
- Trial visits occurred every ~3 months in the LTE

Figure 1. Study design.



*Data from the Phase 2 index trial have been published in *Diabetes Obes Metab.*[2] †Data from the Phase 3 trial have been published in *Lancet Diabetes Endocrinol.*[3] ‡Not all patients received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. LTE, long-term extension; QD, once daily.

Outcomes

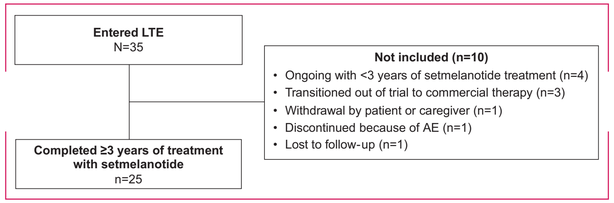
- Outcomes were assessed after yearly intervals of setmelanotide treatment across the index and LTE trials in patients who achieved clinically meaningful response at 1 year of the index trial and who had 3-year on-treatment measurements
  - Clinically meaningful weight response was defined as ≥10% weight reduction for patients aged ≥18 years at baseline
  - Clinically meaningful weight response was defined as ≥0.3-point reduction in body mass index (BMI) Z score for patients aged <18 years at baseline
- Adverse events (AEs) were evaluated

Results

Patient disposition and baseline characteristics

- Overall, 35 patients had a clinically meaningful age-appropriate weight response at 1 year in the index trial and entered the LTE, and 25 were included in this analysis
  - Ten patients were not included in this analysis (Figure 2)
- As of June 13, 2023, 25 patients had measurements at 3 years and were included in this analysis (Table 1)

Figure 2. Patient disposition.



AE, adverse event; LTE, long-term extension.

Table 1. Characteristics at Index Trial Baseline

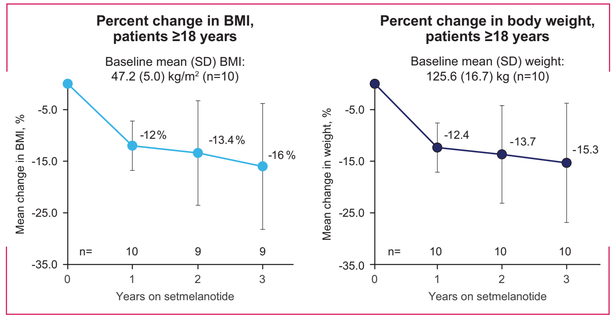
	Patients (n=25)
Age, mean (SD; range), years	21.4 (13.62; 7-61)
Age range, n (%), years	
≥18	10 (40.0)
<18	15 (60.0)
Sex, n (%)	
Male	9 (36.0)
Female	16 (64.0)
Race	
White	22 (88.0)
Black or African American	1 (4.0)
Other	2 (8.0)
Weight, mean (SD), kg	108.3 (29.2)
BMI, mean (SD), kg/m^2	41.7 (9.2)
BMI Z score, mean (SD)*	3.1 (1.4)
%BMI95, mean (SD), percentage points*	147.2 (37.0)
Waist circumference, mean (SD), cm	115.3 (18.7)

BMI, body mass index; %BMI95, percent of the 95th BMI percentile; SD, standard deviation. *Calculated based on Centers for Disease Control and Prevention (CDC) 2022 methodology for children (aged <18 years) only (n=15).

Efficacy outcomes

- Adult patients had a mean (standard deviation [SD]) percent change in BMI of −16.0% (12.2%; range, −43.4% to −4.3%) at Year 3 (Figure 3A)
  - The mean (SD) change in weight in adult patients was −15.3% (11.5%; range, −43.2% to −5.5%) (Figure 3B)

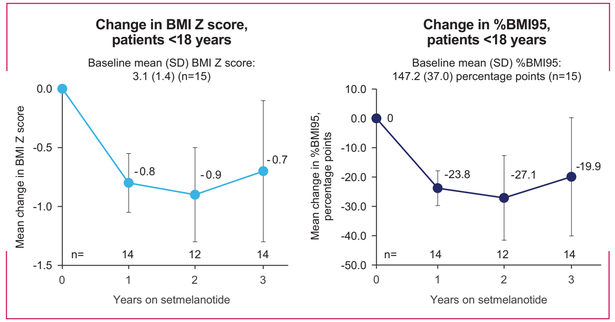
Figure 3. Mean percent change in BMI and body weight.



Error bars are the SD. BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

- Pediatric patients had a decrease in mean (SD) BMI Z score (0.7 [0.60]; range, −1.6 to 0.4) and %BMI95 (19.9 [20.2] percentage points; range: −57.0 to 13.9 percentage points) at Year 3 (Figure 4)

Figure 4. Mean percent change in BMI Z score and %BMI95.



Error bars are the SD. %BMI95, percent of the 95th BMI percentile; BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

Safety outcomes

- No new safety concerns emerged during long-term treatment, and setmelanotide was generally well tolerated in both the index and LTE trials (N=54); the most common AE was skin hyperpigmentation (Table 2)

Table 2. Adverse Events Occurring During the Index and LTE Trials (Safety Population)*

	Patients, n (%) (N=54)
Any AEs	54 (100)
Any treatment-related AEs	54 (100)
Serious treatment-related AEs	1 (1.9)
AEs leading to study drug discontinuation	4 (7.4)
Common AEs (≥20%)	
Skin hyperpigmentation	36 (66.7)
Injection site erythema	30 (55.6)
Injection site pruritus	27 (50.0)
Injection site bruising	21 (38.9)
Injection site induration	20 (37.0)
Nausea	19 (35.2)
Vomiting	17 (31.5)
Injection site pain	16 (29.6)
Headache	14 (25.9)
Injection site edema	13 (24.1)
Diarrhea	13 (24.1)

AE, adverse event. *Data as of October 29, 2022; includes all patients enrolled in the index and LTE trials (n=54) and represents an earlier data cut than efficacy data.

Conclusions

- Up to 3 years of treatment with the MC4R agonist setmelanotide was associated with clinically relevant reductions in age-appropriate weight-related measures in pediatric and adult patients with BBS
- No new safety concerns were identified with long-term use of setmelanotide
- Limitations of this study include the lack of a control group and small sample sizes
- These data support the continued efficacy and long-term use of setmelanotide in patients with BBS

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