Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome

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Summary

- **Setmelanotide demonstrated continued clinical benefit on body weight–related outcomes in patients with Bardet-Biedl syndrome (BBS) for up to 2 years**

Introduction

- BBS is a rare genetic disease of obesity characterized by multiorgan dysfunction; severe, early-onset obesity; and insatiable pathologic hunger (hyperphagia)[1]
- Genetic variants in BBS-associated genes can be associated with impairment of the melanocortin pathway through impaired leptin receptor trafficking and reduced proopiomelanocortin expression[2,3]
- The melanocortin-4 receptor agonist setmelanotide produced beneficial reductions in weight, body mass index (BMI), and hunger in patients with BBS after ~1 year in Phase 2 and 3 clinical trials[1,4]
- There is an unmet need for targeted treatments for obesity and hyperphagia with long-term efficacy in patients with BBS[5]
- The long-term effects of setmelanotide have not yet been characterized for patients with BBS

Objective

- To assess the continued long-term efficacy of setmelanotide treatment in patients with BBS over ~2 years

Methods

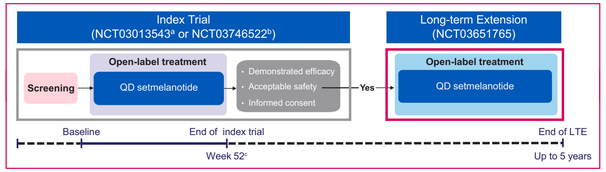
Trial Design

- 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 based on efficacy results
- Patients with BBS enrolled in the LTE after completing Phase 2 or 3 trials of setmelanotide[1,4]
  - Patients received up to 15 months of setmelanotide treatment as a part of their index trial
  - At the time of index trial enrollment, patients were ≥6 years old with obesity
- Patients began the LTE immediately following completion of an index trial and continued on the same dose of setmelanotide (Figure 1)
- Trial visits occurred approximately every 3 months in the LTE

Outcomes

- Outcomes were assessed after ~2 years of setmelanotide treatment across the index and LTE trials
- Changes in body weight measures relative to index trial baseline as well as adverse events were evaluated
- Weight-related measures were analyzed by adult (≥18 years) and pediatric (<18 years) subgroups separately to minimize the confounding and dilution of treatment effect of including pediatric patients who were still growing with the adult population
  - Evaluation of weight-related measures that may be more appropriate for each age group for characterizing and monitoring changes in obesity was prioritized
    - In the overall population, changes in BMI are reported
    - In adults, changes in weight are reported; in pediatric patients, BMI Z score and percentage of the BMI 95th percentile (%BMI_{95}) are reported

Figure 1. Study design.



[a]Data from the Phase 2 index trial have been published in *Diabetes Obes Metab*.[1] [b]Data from the Phase 3 trial were previously presented at ObesityWeek®; November 1-5, 2021; Virtual.[4] [c]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.

Results

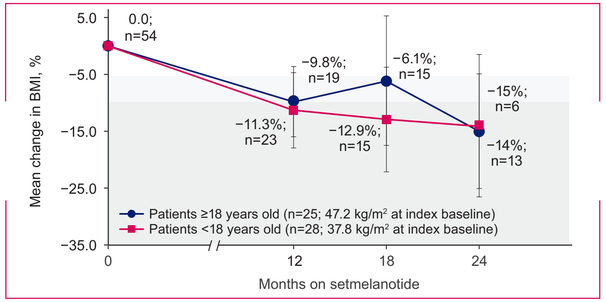
Participant Disposition and Baseline Characteristics

- As of October 29, 2022, 54 patients with BBS enrolled in an index trial (<18 years old, n=28; ≥18 years old, n=26), of whom 42 continued into the LTE
- Among patients entering the LTE, 30 and 19 received at least 18 and 24 months of setmelanotide treatment, respectively
  - During the LTE, 4 patients discontinued from the study because of patient withdrawal (n=3) or adverse event (n=1)
  - 38 patients were receiving ongoing treatment at the time of analysis, and not all patients have reached the 18-, 24-, and 36-month time points
- At index trial baseline, mean (standard deviation [SD]) BMI for all patients was 42.2 (9.2) kg/m^2 (n=53)
  - Mean (SD) body weight in patients aged ≥18 years (n=25) was 132.3 (20.9) kg
  - Mean (SD) BMI Z score and %BMI_{95} in patients aged <18 years (n=28) was 3.51 (0.76) and 150.0% (34.5%), respectively
  - The mean (SD) age of patients was 20.4 (11.8) years; 55.6% of patients were female

Efficacy Outcomes

- Mean (SD) BMI was 44.2 kg/m^2 (9.2) at index trial baseline, with a percent change in BMI across all patients at 18 and 24 months of setmelanotide treatment of −9.5% (10.5%; n=30) and −14.3% (11.6%; n=19), respectively (Figure 2)

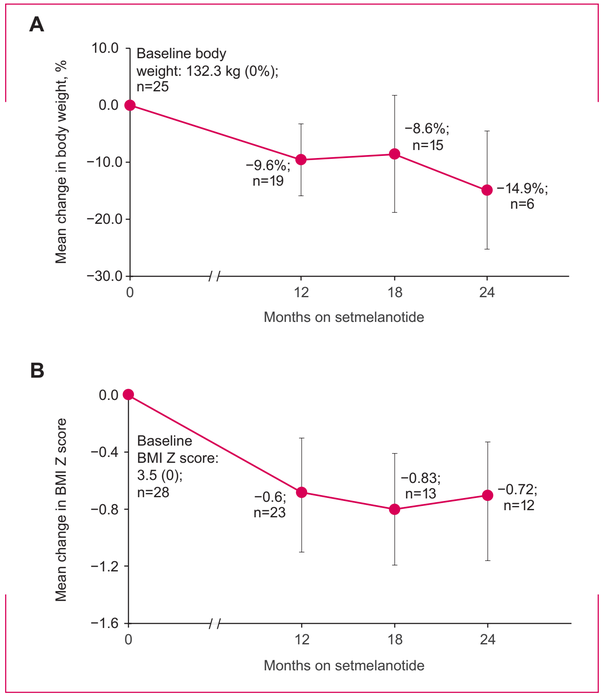
Figure 2. Mean percent change in BMI from index trial baseline by months of setmelanotide treatment in all patients with BBS.



Error bars indicate standard deviation. Shading represents benchmarks of −5% and −10% change. BBS, Bardet-Biedl syndrome; BMI, body mass index.

- Patients aged ≥18 years had a mean (SD) body weight of 132.3 (20.9) kg and exhibited a percent change in body weight of −8.6% (10.3%; n=15) and −14.9% (10.4%; n=6) after 18 and 24 months of treatment, respectively (Figure 2A)
  - Six of 15 patients (40.0%) and 5 of 6 patients (83.3%) achieved ≥10% weight reduction at Month 18 and 24, respectively
- Patients aged <18 years had a mean (SD) BMI Z score of 3.5 (0.8) and exhibited a change in BMI Z score of −0.83 (0.50; n=13) and −0.72 (0.54; n=12) after 18 and 24 months of treatment, respectively (Figure 3B)
  - All patients <18 years of age had a BMI Z score reduction of ≥0.2 points
  - Twelve of 13 patients (92.3%) and 9 of 12 patients (75.0%) <18 years of age achieved BMI Z score reductions of ≥0.3 points at Month 18 and 24, respectively
- In patients aged <18 years, mean (SD) absolute change in %BMI_{95} was −23.4% (11.8%; n=15) and −29.8% (22.4%; n=13) at Month 18 and 24, respectively

Figure 3. (A) Mean percent change in body weight from index trial baseline by months of setmelanotide treatment in patients ≥18 years old. **(B)** Mean change in BMI Z score from index trial baseline by months of setmelanotide treatment for patients <18 years old.



Error bars indicate standard deviation. BMI, body mass index.

Safety Outcomes

- Adverse events in the overall safety population across the index and LTE trials (N=54) are reported in the Table

Table. Adverse Events Occurring During the Index and LTE Trials in the Safety Population (N=54)

	n (%)
TEAEs	54 (100)
Treatment-related TEAEs	54 (100)
Serious treatment-related TEAEs	1 (1.9)
TEAEs leading to study drug withdrawal	4 (7.4)
Common TEAEs (≥20%)	
Skin hyperpigmentation	36 (66.7)
Injection site erythema	30 (56.6)
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)
Diarrhea	13 (24.1)
Injection site edema	13 (24.1)

LTE, long-term extension; TEAE, treatment-emergent adverse event.

- Setmelanotide treatment was generally well tolerated across the index and LTE trials; the most common adverse event was skin hyperpigmentation
- During the LTE, 1 patient with BBS discontinued because of an adverse event (auditory hallucination) that was determined unlikely to be related to setmelanotide
- No new safety concerns emerged during long-term treatment

CONCLUSIONS

- Up to 2 years of setmelanotide treatment was associated with reduction in body weight–related measures and maintained weight-related improvements in adult and pediatric patients with BBS, with no new safety concerns
- Further evaluation of the effect of different characteristics (eg, age, sex, genotype) on setmelanotide response is ongoing
- This trial supports the continued efficacy and long-term use of setmelanotide in patients with BBS

[†]Robert S. Mittleman was an employee at Rhythm Pharmaceuticals, Inc. at the time of abstract submission.

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