Setmelanotide Treatment in Pediatric and Adolescent Patients With Bardet-Biedl Syndrome and Severe Obesity

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Summary

- **Outcomes from this Phase 3 trial demonstrate treatment with setmelanotide is associated with clinically beneficial reduction in body weight and hunger in pediatric and adolescent patients with Bardet-Biedl syndrome (BBS)**
- **The results presented here highlight the potential of setmelanotide for early intervention in patients with BBS and severe obesity**

Introduction

- BBS is a rare genetic syndromic obesity with hyperphagia, or insatiable hunger, and early-onset obesity that progresses over time, in addition to other clinical manifestations[1,2]
- Symptoms of BBS are associated with impairments in cilia function, and include impairments to leptin-melanocortin signaling, which regulates energy balance[3]
- Early intervention is important because BBS is associated with progressive obesity throughout childhood[2]
- In a Phase 3 trial, the melanocortin-4 receptor agonist setmelanotide demonstrated clinically beneficial reductions of body weight and hunger scores in patients with BBS[4]

Objective

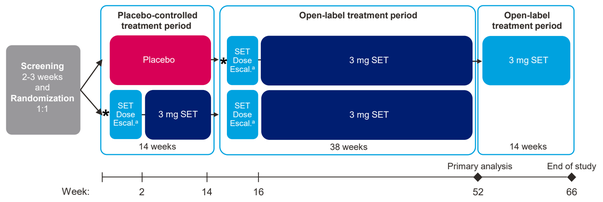
- To report the efficacy and safety of setmelanotide in the subgroup of pediatric and adolescent patients with BBS from a Phase 3 trial

Methods

Study Design

- The efficacy and safety of setmelanotide on body weight and hunger in patients with BBS were evaluated in a multicenter Phase 3 clinical trial that included a double-blind placebo-controlled period (NCT03746522) (Figure 1)[5]

Figure 1. Study Design



Asterisks represent start of active treatment for each study group. †Dose escalation was performed according to age at baseline. Patients <16 years of age were administered 1 mg QD of setmelanotide for the first week and 2 mg QD for the second week, and patients ≥16 years of age were administered 2 mg QD for 2 weeks; both age groups were escalated to 3 mg at the start of week 3. At the time of the primary analysis, a multiple imputation model was implemented to estimate data for patients who had not yet received <52 weeks of setmelanotide. Escal., escalation; QD, once daily; SET, setmelanotide.

Key Eligibility Criteria

- Eligible patients had a confirmed BBS diagnosis and obesity, defined as weight >97th percentile for age and sex in patients <16 years of age or body mass index (BMI) ≥30 kg/m^2 for patients ≥16 years of age
- Patients were excluded if they had recently experienced >2% weight loss, had recently used obesity medication, had prior exposure to setmelanotide, exhibited moderate-to-severe renal dysfunction (glomerular filtration rate <30 mL/min), or had prior gastric bypass surgery resulting in >10% weight loss with no evidence of weight regain

Key Endpoints

- The primary endpoint was the proportion of all patients who had achieved ≥10% reduction in body weight after 52 weeks of setmelanotide
- Key secondary endpoints for the full (adult and pediatric/adolescent) cohort included the proportion of patients who achieved ≥25% reduction in daily hunger score, mean percent change in hunger, and mean percent change in body weight after 52 weeks of setmelanotide treatment (all endpoints were achieved and were previously presented virtually at ObesityWeek®, November 1-5, 2021)
  - Hunger was assessed in patients ≥12 years of age on the basis of the daily hunger questionnaire using a scale ranging from 0 = not hungry at all to 10 = hungriest possible
- Efficacy outcomes evaluated in the pediatric and adolescent population were change from baseline at Week 52 for BMI, BMI Z score, and percent of BMI 95th percentile (%BMI$_{95}$); safety was assessed on the basis of adverse events

Results

Patient Disposition and Baseline Characteristics

- There were 32 pivotal patients with BBS enrolled in this trial, among whom 16 were <18 years old (Table 1)

Table 1. Baseline Characteristics of Pediatric and Adolescent Patients

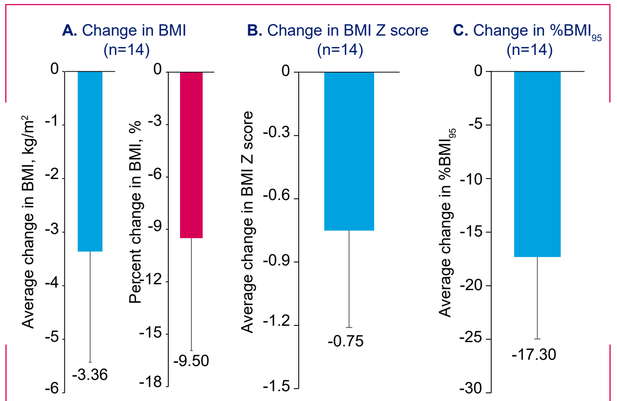
	Patients (n=16)
Randomization, n (%)	
Setmelanotide	9 (56)
Placebo	7 (44)
Age, mean (SD) [range], y	12.31 (2.12) [7-16]
Male-to-female ratio	50:50
Race, n (%)	
Black or African American	1 (6.3)
White	14 (87.5)
Other	1 (6.3)
Weight (ATB), mean (SD) [range], kg	98.37 (29.45) [49.3-173.8]
BMI (ATB), mean (SD) [range], kg/m^2	34.77 (9.44) [24.4-61.4]
BMI Z score (ATB), mean (SD) [range]	3.74 (1.34) [1.8-7.1]

ATB, active treatment baseline; BMI, body mass index; SD, standard deviation. *ATB, N=16.

Efficacy Outcomes

- After 52 weeks of treatment, pediatric and adolescent patients experienced a mean (standard deviation [SD] ,95% confidence interval [CI]) change from baseline of –3.36 (2.07; −4.6, −2.2) kg/m^2 for BMI (n=14), –0.75 (0.458; 95% CI, −1.02, −0.49) for BMI Z score (n=14), and –17.30 (7.67; 95% CI, −21.73, −12.87) for %BMI$_{95}$ (n=14) (Figure 2)

Figure 2. Changes in pediatric weight metrics at Week 52.



Error bars are the standard deviation. %BMI$_{95}$, percent of BMI 95th percentile; BMI, body mass index.

- Twelve of 14 patients (85.7%) achieved ≥0.2-point improvement in BMI Z score, with 10 of 14 patients (71.4%) achieving ≥0.3-point improvement
- Reduction in weight-related measures was observed in the youngest age group (6-11 years old), with BMI Z score changes ranging from −0.3 to −1.2 and BMI 95th percentile changes ranging from −6.8 to −24.3
- Table 2 reports the individual changes in the weekly average of daily hunger scores after 52 weeks of treatment for patients ≥12 to <18 years of age without cognitive impairment
  - There were 3 patients (75%) who achieved 25% improvement in weekly average of daily hunger scores after 52 weeks of treatment

Table 2. Change in Pediatric Hunger Scores After 52 Weeks of Treatment

Participant age	ATB score	Score after ≤52 weeks of treatment[a]	Change from ATB, absolute change (%)
12	5	3.2	-1.8 (-36)
14	5.6	2	-3.6 (-64.1)
13	5.3	3.7	-1.6 (-30.2)
12	10	8[b]	-2 (-20)

Hunger scores are reported as the weekly average of daily maximal hunger scores for patients ≥12<18 years of age. [a]All data report hunger after 52 weeks of treatment unless otherwise noted. [b]Patient withdrew at 18 weeks of setmelanotide treatment; reported value is at 18 weeks of treatment. ATB, at treatment baseline.

Safety Outcomes

- Setmelanotide treatment was generally well tolerated, with only 1 adverse event (AE) (nausea and vomiting) leading to study drug discontinuation (Table 3)
- The most common AEs were skin hyperpigmentation, vomiting, and injection site–related complications

Table 3. Treatment-Related AEs in Patients <18 Years of Age

	N (%)
At least 1 AE	16 (100)
Serious AEs	0 (0)
AEs leading to discontinuation	1 (6.3)
Common AE (≥25%)	
Skin hyperpigmentation	12 (75)
Vomiting	7 (43.8)
Nausea	4 (25)
Injection site erythema	10 (62.5)
Injection site pain	7 (43.8)
Injection site pruritus	6 (37.5)
Injection site bruising	5 (31.3)
Injection site induration	4 (25)
Headache	4 (25)

Treatment-related treatment-emergent AEs reported. AE, adverse event.

Conclusions

- Setmelanotide treatment resulted in clinically beneficial reductions in pediatric weight and hunger-related outcomes and exhibited an acceptable safety and tolerability profile in pediatric and adolescent patients with BBS
  - Reductions in weight-related measures in the youngest age group (aged 6-11 years) highlight the utility of early intervention
- The data presented underscore setmelanotide treatment as an efficacious intervention for severe obesity and hyperphagia in patients with BBS

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