Exploration of Clinical Improvements Following Setmelanotide Treatment in Patients With Bardet-Biedl Syndrome

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Summary

- **Most patients with Bardet-Biedl syndrome (BBS) had clinically meaningful improvements in weight, hunger, or quality of life (QOL) after setmelanotide treatment, suggesting clinical benefit may extend beyond weight loss**

Introduction

- In patients with BBS, signaling defects in the melanocortin-4 receptor (MC4R) pathway may lead to hyperphagia (pathological, uncontrollable hunger) and severe obesity, which can negatively affect QOL[1,2]
- In BBS, weight gain typically develops in early childhood and progresses over time[3]; therefore, weight reduction or stabilization could alleviate the negative impacts of obesity
- Setmelanotide, an MC4R agonist that restores MC4R pathway signaling,[4] is an approved treatment option in the United States and European Union for chronic weight management and control of hunger in adult and pediatric patients aged 6 years and older with syndromic obesity due to BBS[5,6]
- In a randomized placebo-controlled Phase 3 trial (NCT03746522) in patients with BBS or Alström syndrome setmelanotide reduced body weight by ≥10% in 32.3% of patients aged ≥12 years (n=31; *P*=0.0006) after 1 year (primary endpoint)[7]
  - All patients in this analysis meeting the primary endpoint were patients with BBS

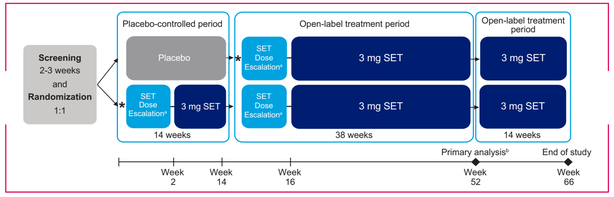
Objective

- To investigate clinical benefit following setmelanotide treatment in a Phase 3 trial of patients with BBS by measuring changes in weight-related measures, hunger, and QOL

Methods

- A Phase 3 trial (NCT03746522) investigated the effects of 1 year of setmelanotide on obesity and hunger in patients aged ≥6 years with BBS or Alström syndrome; patients received double-blind setmelanotide or placebo treatment for 14 weeks followed by open-label setmelanotide for ≥52 weeks of total setmelanotide treatment (Figure)[8]
  - This post hoc analysis focuses on clinical outcomes in patients with BBS

Figure. Study design.



Efficacy outcomes are reported relative to active treatment baseline (denoted by the asterisk) for each study group (ie, Week 0 for the setmelanotide group and Week 14 for the placebo group). *During dose escalation, participants ≥16 years of age received setmelanotide 2 mg QD for 2 weeks, patients <16 years of age received setmelanotide 1 mg QD for 1 week and 2 mg QD for 1 week, and all participants received 3 mg QD at the beginning of Week 3. For patients who received ≥52 weeks of setmelanotide treatment by end of study, the analysis was performed at 52 weeks of setmelanotide treatment. [b]A multiple imputation model was used to impute data for patients who received <52 weeks of setmelanotide at the primary analysis timepoint. QD, once daily; SET, setmelanotide.

- In this analysis, outcomes were assessed at the patient level at the last study visit
- Adverse events were also assessed

Weight-related measures

- Body weight change for adults (clinically meaningful improvement defined as ≥5% reduction)[9]
- Body mass index (BMI) Z score for pediatric patients (clinically meaningful improvement defined as ≥0.2-point decrease)[10]
- Percentage of the 95th BMI percentile for pediatric patients (clinically meaningful improvement defined as ≥5-point decrease in percentile)[11]
- Patients who showed a nonmeaningful decrease in change in weight-related measures were considered to have disease stabilization

Hunger-related measures

- Hunger was assessed using an 11-point Likert scale in patients ≥12 years old without cognitive impairment
  - Daily maximal hunger was self-reported using a numerical rating scale ranging from 0 to 10, with 0 = "not hungry at all" and 10 = "hungriest possible" (clinically meaningful improvement defined as ≥1-point reduction)

QOL-related measures

- QOL was assessed in adults and pediatric patients using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and Pediatric Quality of Life Inventory (PedsQL), respectively[12,13]
  - For PedsQL, age-appropriate assessment tools (PedsQL-Child [for those 8-12 years old] and PedsQL-Teen [for those 13-17 years old]) were used, and outcomes were reported together (clinically meaningful improvement was defined as a total score change >4.4 points[13])
  - For IWQOL-Lite, impairment was defined on the basis of the total score, with definitions for severe (<71.8), moderate (71.9-79.4), mild (79.5-87.0), or no (87.1-94.6) impairment (clinically meaningful improvement was defined as a total score change ranging from 7.7 to 12 points[12])
- Patients who showed a nonmeaningful improvement in QOL-related measures were considered to have disease stabilization

Results

- Sixteen adults (age range, 19-44 years) (Table 1) and 16 pediatric patients (age range, 7-16 years) (Table 2) with BBS were enrolled in the trial and evaluated
  - Treatment time on setmelanotide ranged from 14 to 67 weeks (Tables 1 and 2)
- Twenty-seven of 32 patients (84%) had improvements that met clinically meaningful thresholds in ≥1 measure at the last study visit (Table 1 and 2)
  - Of the 5 patients without clinically meaningful improvement, 3 showed weight stabilization (Table 1 and 2)
- Overall, 30 of 32 patients (94%) experienced clinical improvement or weight stabilization (Tables 1 and 2)
  - In adult patients, 14 of 16 (87.5%) experienced clinical improvement or weight stabilization (Table 1)
  - All pediatric patients experienced clinical improvement or weight stabilization (Table 2)
- Overall, 10 of 11 evaluable patients (90.9%) experienced ≥1-point reduction in maximal hunger score (Tables 1 and 2)
  - In adult patients, 7 of 8 (87.5%) experienced ≥1-point reduction in maximal hunger score (Table 1)
  - All pediatric patients (n=3) experienced ≥1-point reduction in maximal hunger score (Table 2)
- Overall, 18 of 19 evaluable patients (94.7%) experienced a meaningful or positive nonmeaningful (no change from baseline) improvement in QOL (Tables 1 and 2)
  - All evaluable adult patients experienced a meaningful or positive nonmeaningful improvement in QOL (Table 1)
  - In evaluable pediatric patients, 8 of 9 (88.9%) experienced a meaningful or positive nonmeaningful improvement in QOL (Table 2)

Table 1. Clinical Outcomes[a] With Setmelanotide in Patients With BBS Aged ≥18 Years

Age at study entry, years	Weeks on study at last visit	Gene mutation	Weight, percent change	BMI, percent change	Most/Worst hunger score change[b]	Quality of life improvement[c]
43	66	*BBS10*	-13.7	-13.4	0.0	Yes
44	65	*BBS2*	-15.1	-15.1	NA	NMI
34	65	*BBS1*	-11.1	-11.1	NA	–
21	66	*BBS1*	-14.4	-13.2	-2.0	Yes
19	66	BBS related	-9.1	-8.3	-3.0	Yes
42	66	*BBS10*	-5.1	-8.0	-4.0	Yes
20	66	*BBS1*	+5.3	+4.8	-4.0	NMI
19	19	*BBS1*	+9.2	+9.2	NA	–
20	66	BBS related	-16.7	-16.7	-2.0	Yes
28	67	*BBS1*	-5.2	-4.3	–	NMI
27	14	Not confirmed	-2.1	-2.1	–	–
29	66	Not confirmed	-15.8	-14.8	-5.0	Yes
34	24	Not confirmed	-5.0	-5.0	–	–
24	71	BBS related	-4.4	-4.4	NA	NMI
22	66	BBS related	-7.2	-7.2	NA	–
22	50	BBS related	-7.2	-7.2	-2.0	–

"–" denotes missing data, gray shading denotes no improvement, dark-blue shading denotes clinically meaningful improvement, and light-blue shading denotes nonmeaningful improvement. [a]Disease stabilization assessed for weight- and quality of life–related measures. [b]Hunger was not assessed in patients with cognitive impairment. [c]At Week 52. BBS, Bardet-Biedl syndrome; BMI, body mass index; NA, not applicable (ie, hunger not assessed owing to cognitive impairment); NMI, nonmeaningful improvement.

- The most frequent adverse events (≥25% of patients) included skin hyperpigmentation (56.3%), injection site erythema (50.0%), injection site pruritus (34.4%), nausea (34.4%), injection site bruising (34.4%), injection site pain (31.3%), vomiting (28.1%), and injection site induration (25.0%)
- One patient experienced a serious adverse event of anaphylaxis while receiving placebo that was determined to be related to treatment

Table 2. Clinical Outcomes[a] With Setmelanotide in Patients With BBS Aged <18 Years

Age at study entry, years	Weeks on study at last visit	Gene mutation	BMI Z score change	BMI 95th percentile percentage point change	Most/Worst hunger score change[b]	Quality of life improvement[c]
12	65	*BBS10*	−0.80	−17.1	–	–
10	66	*BBS1*	−1.26	−22.6	NA	–
12	66	*BBS10*	−2.18	−34.8	–4.0	Yes
15	66	*BBS10*	−1.22	−33.7	–	–
12	27	*BBS1*	−0.38	−9.8	NA	–
7	65	*BBS1*	−0.95	−18.7	–	–
14	66	*BBS10*	−0.07	−6.7	–5.0	NMI
10	65	BBS related	−0.30	−6.8	–	Yes
14	64	*BBS10*	−0.85	−23.9	NA	–
16	65	BBS related	−0.07	−4.9	NA	NMI
13	64	BBS related	−0.33	−8.0	NA	Yes
12	65	BBS related	−0.69	−21.5	NA	Yes
13	65	BBS related	−1.00	−29.1	–	Yes
13	65	*BBS1*	−0.96	−12.8	–1.0	Worsened
12	67	*BBS6*	−0.94	−26.7	–	Yes
12	17	Not confirmed	−0.18	−4.3	–	–

"–" denotes missing data, gray shading denotes no improvement, dark-blue shading denotes clinically meaningful improvement, and light-blue shading denotes nonmeaningful improvement. [a]Disease stabilization assessed for weight- and quality of life–related measures. [b]Hunger was not assessed in patients <12 years old or in those with cognitive impairment. [c]At Week 52. BBS, Bardet-Biedl syndrome; BMI, body mass index; NA, not applicable (ie, hunger not assessed owing to cognitive impairment and/or patient aged <12 years); NMI, nonmeaningful improvement.

Conclusions

- Most patients with BBS showed clinical benefit following setmelanotide treatment, as measured by decreases in age-appropriate weight-related measures, decreases in hunger, and overall improvements in QOL
- Assessing hunger and QOL changes during this clinical trial provided additional information to better assess improvement of the multifaceted disease burden in these patients
  - Clinical improvements beyond weight loss should be assessed in patients with BBS

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