Efficacy and Safety of the Melanocortin-4 Receptor Agonist Setmelanotide in Obesity Due to Bardet-Biedl Syndrome: a Phase 3 Trial

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Summary

- In this Phase 3 trial, setmelanotide was associated with significant body weight and hunger reduction in individuals with Bardet-Biedl syndrome (BBS)
- Setmelanotide was a well-tolerated treatment, and no new safety concerns emerged
- On the basis of these and earlier Phase 2 results,[1] setmelanotide may represent a novel treatment for obesity in individuals with BBS
- Further evaluation of setmelanotide in individuals with Alström syndrome is needed to determine the efficacy in this syndrome

Introduction

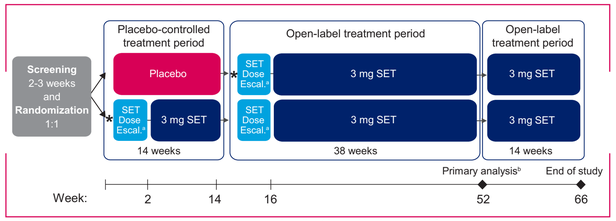
- In individuals with BBS, dysfunction in the melanocortin-4 receptor pathway has been hypothesized to lead to hyperphagia and obesity[2,3]
- BBS is a rare autosomal pleiotropic and multigenic syndrome involving primary cilia dysfunction[4-6]
- The BBSome, a complex of 8 proteins, is a contributor to the regulation of energy balance by anorexigenic proopiomelanocortin neurons and orexigenic agouti-related peptide neurons[7]
- Setmelanotide is a melanocortin-4 receptor agonist that was previously shown to reduce hunger and body weight and have a favorable safety profile in participants with BBS in a Phase 2 trial[1]

Methods

Objective/Study Design

- This multicenter, placebo-controlled plus open-label Phase 3 clinical trial (NCT03746522) was designed to evaluate the effect of setmelanotide on body weight and hunger in participants (aged ≥6 years) with syndromic obesity related to BBS or Alström syndrome (Figure 1)

Figure 1. 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). [a]During dose escalation, participants ≥16 years of age received setmelanotide 2 mg QD for 2 weeks, participants <16 years of age received setmelanotide 1 mg QD for the first week and 2 mg for the second week, and all participants received 3 mg at the beginning of Week 3. [b]A multiple imputation model was used to impute data in participants who received <52 weeks of setmelanotide at the time of the primary analysis. Escal., escalation; QD, once daily; SET, setmelanotide.

Key Entry Criteria

- Obesity was defined as body mass index ≥30 kg/m^2 (in those aged ≥16 years) or weight >97th percentile (in those aged 6–15 years)
- Participants were excluded if they had recently experienced weight loss, had recent use of obesity medication, or ever received setmelanotide

Endpoints and Assessments

- The primary endpoint was the proportion of participants (≥12 years) who achieved ≥10% reduction in body weight from baseline after 52 weeks of setmelanotide treatment
- Key secondary endpoints further assessed changes in hunger (in participants without cognitive impairment) and body weight
  - Daily maximal hunger score was based on participant responses to scoring their "most" hunger during the day using a numerical rating scale ranging from 0 to 10, where 0 = not hungry at all and 10 = the hungriest possible

Results

Participant Disposition and Baseline Characteristics (Table 1)

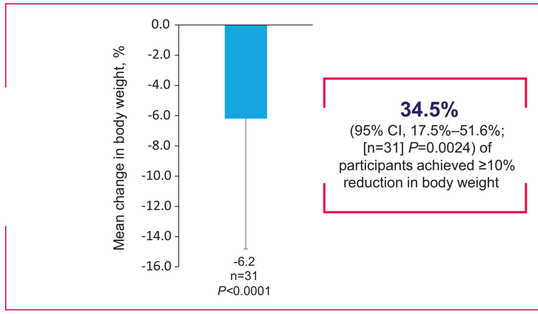
Table 1. Baseline Participant Characteristics

	Participants (N=38)
Randomization, n (%)	
Setmelanotide	19 (50.0)
Placebo	19 (50.0)
Genotype, n (%)	
BBS	32 (84.2)
Alström syndrome	6 (15.8)
Age, mean (SD) [range], y	19.8 (10.2) [7–44]
Male to female ratio	15:23
Race, n(%)	
Asian	1 (2.6)
Black or African American	3 (7.9)
White	31 (81.6)
Other	3 (7.9)
Ethnicity, n (%)	
Hispanic or Latino	1 (2.6)
Not Hispanic or Latino	37 (97.4)
Weight, mean (SD) [range], kg	112.0 (31.0) [49.3–191.8][a]
BMI, mean (SD) [range], kg/m^2	42.2 (11.1) [24.4–83.0][a]
BMI Z score, mean (SD) [range]	3.74 (1.3) [1.8–7.1][b]

[a]Active treatment baseline, n=36. [b]Active treatment baseline, among participants <18 years old, n=16. BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

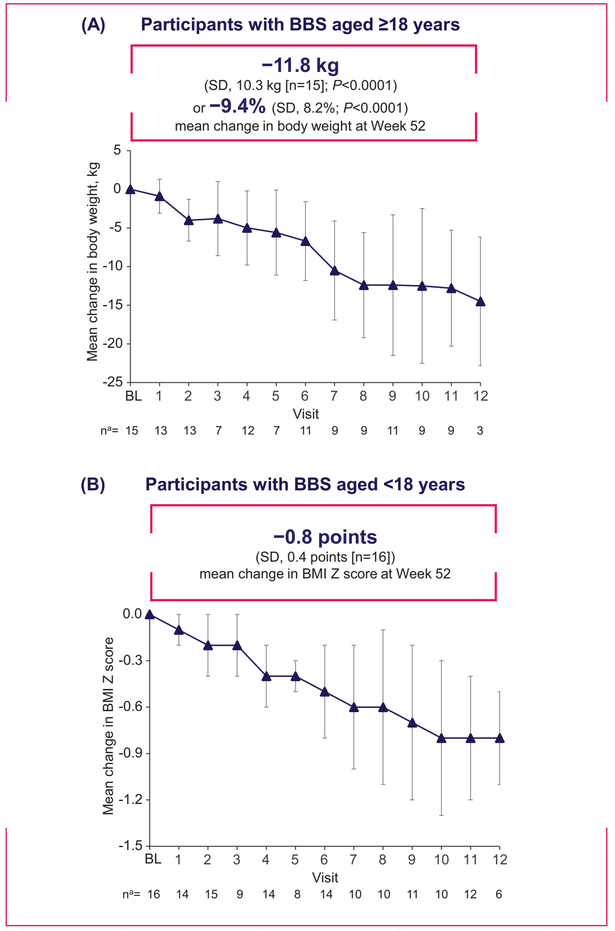
Efficacy Outcomes (Figures 2-4)

Figure 2. Change in body weight in participants aged ≥12 years after 52 weeks of treatment.



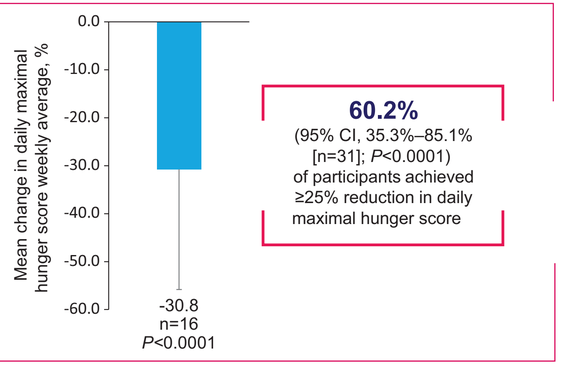
Error bar is the standard deviation. CI, confidence interval.

Figure 3. (A) Mean change in body weight among participants with BBS aged ≥18 years after 52 weeks of treatment, and **(B)** mean change in BMI Z score among participants with BBS aged <18 years after 52 weeks of treatment.



[a]Data shown by study visit do not include data imputed for participants who received <52 weeks of setmelanotide at the time of the primary analysis. Error bars are the standard deviation (SD). BBS, Bardet-Biedl syndrome; BL, baseline; BMI, body mass index.

Figure 4. Change in daily maximal hunger score in participants aged ≥12 years without cognitive impairment after 52 weeks of treatment.



Error bar is the standard deviation. CI, confidence interval.

Safety Outcomes (Table 2)

Table 2. Treatment-Related AEs[a]

	Participants, n (%)
At least 1 AE	37 (97.4)
Serious AE	1 (2.6)
AE leading to study withdrawal[b]	5 (13.2)
Common AEs (≥15%)	
Skin hyperpigmentation	22 (57.9)
Injection site erythema	16 (42.1)
Injection site pain	11 (28.9)
Injection site pruritus	11 (28.9)
Injection site bruising	9 (23.7)
Injection site induration	8 (21.1)
Nausea	7 (18.4)

[a]Treatment-related treatment-emergent AEs reported; safety analysis set, N=38. [b]AEs are treatment emergent and include nausea, vomiting, and anaphylactic reaction (in a participant receiving placebo during the placebo-controlled period).
AE, adverse event.

- There was 1 serious adverse event of anaphylactic reaction among all participants (n=38) that was considered related to treatment during this participant's placebo-controlled period

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