Phase 3 Trial of Setmelanotide in Participants With Bardet-Biedl Syndrome: Placebo-Controlled Results

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Conflict of Interest

Name: Jesús Argente

☐ I have the following potential conflicts of interest to report:

- ☐ Research contracts
- ☐ Consulting
- ☐ Employment in the industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- X Other(s) – *Payment for lectures and participation in advisory board for Rhythm Pharmaceuticals, Inc.*

☐ I declare that I have no potential conflict of interest.

Disclosures

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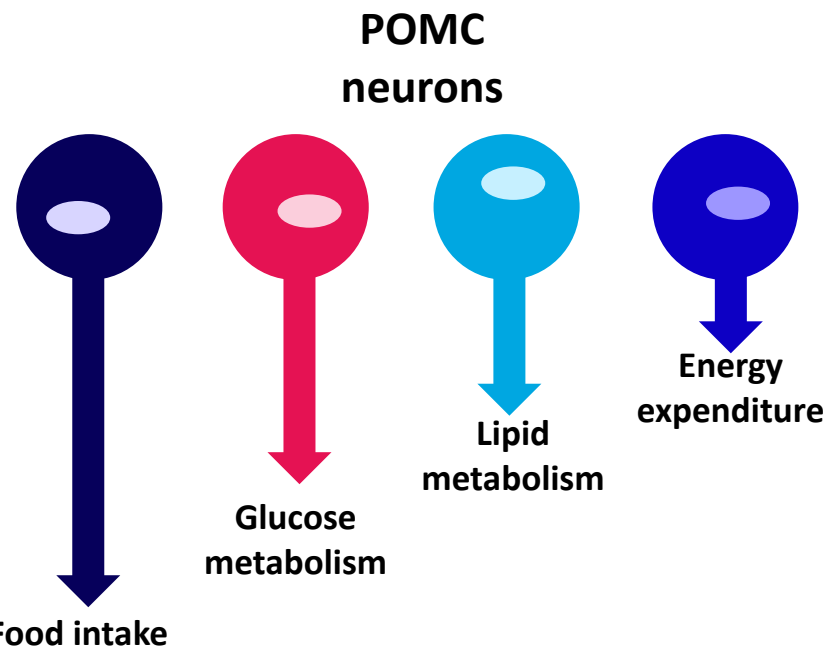
Energy Regulation in Bardet-Biedl Syndrome

- Bardet-Biedl syndrome (BBS) is a rare autosomal pleiotropic and multigenic syndrome involving primary cilia dysfunction[1-3]
- Individuals with variants in BBS-associated genes often present with early-onset, severe obesity and hyperphagia[1,2]
- The BBSome is an important regulator of energy balance required for control of anorexigenic POMC neurons and orexigenic AgRP neurons[4]
- Obesity in BBS may be associated with reduced activation of the MC4R, although the molecular mechanisms are not fully understood[3,5]

Mechanism of energy balance regulation by different POMC neuron populations[6]



AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; BMI, body mass index; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Beales et al. *J Med Genet*. 1999;36:437-446. **2.** Sherafat-Kazemzadeh et al. *Pediatr Obes*. 2013;8:e64-e67. **3.** Forsythe et al. *Eur J Hum Genet.* 2013;21:8-13. **4.** Guo et al. *Diabetes.* 2019;68:1591-1603. **5.** Haws et al. *Diabetes Obes Metab*. 2020;22:2133-2140. **6.** Quarta et al. *Nat Metab.* 2021;3:299-308.

Setmelanotide Treatment Demonstrates Weight and Hunger Benefits After 1 Year in Patients With BBS

- In a preliminary analysis of a Phase 3 trial in BBS and Alström syndrome, 52 weeks of treatment with the MC4R agonist setmelanotide was associated with significant reductions in body weight and hunger[1]
  - All responders were participants with BBS[1]

Body Weight and BMI Z Score Change From Baseline at Week 52 With Setmelanotide: Phase 3 Trial of Individuals With BBS[1]

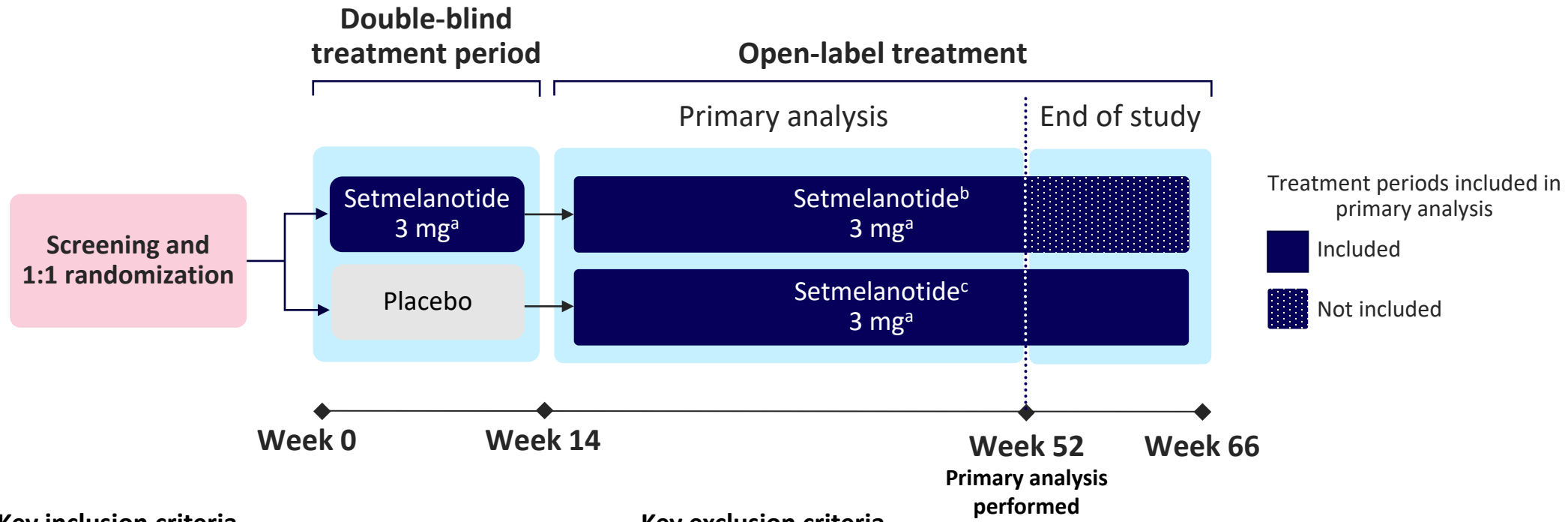
Age group	Metric	Absolute (percent) change at Week 52
Age ≥18 years (n=15)	**Mean body weight**	**−11.8 kg (−9.4%)**
Age <18 (n=16)	**Mean BMI Z score**	**−0.8 (−24.5%)**

The current analysis evaluates setmelanotide compared with placebo in participants with BBS in the initial double-blind, randomized period of the same Phase 3 trial (NCT03746522)

BBS, Bardet-Biedl syndrome; BMI, body mass index; MC4R, melanocortin-4 receptor.

1. Haws et al. Poster presented at: The Endocrine Society Annual Meeting; March 20-23, 2021; Virtual.

Phase 3 Trial to Evaluate Setmelanotide in Individuals With BBS



Key inclusion criteria

- Clinical diagnosis of BBS
- ≥6 years of age
- Obese
  - ≥16 years: BMI ≥30 kg/m^2
  - 6–15 years: weight >97th percentile for age and sex

Key exclusion criteria

- Recent (within 2 months) intensive diet and/or exercise resulting in >2% weight loss
- Use of approved obesity medication within 3 months of randomization
- Prior gastric bypass resulting in >10% weight loss durably maintained
- Glomerular filtration rate <30 mL/min

[a]Dose escalation based on age up to 3.0 mg. [b]For participants who received >52 weeks of setmelanotide at the end of study, analysis is performed for 52 weeks of setmelanotide. [c]A multiple imputation model was used to impute data in participants who received <52 weeks of setmelanotide at the time of the primary analysis.
BBS, Bardet-Biedl syndrome; BMI, body mass index.

Phase 3 Trial Endpoints

Primary endpoint Week 52

- Proportion of participants ≥12 years achieving ≥10% weight loss

Key secondary endpoints Week 52

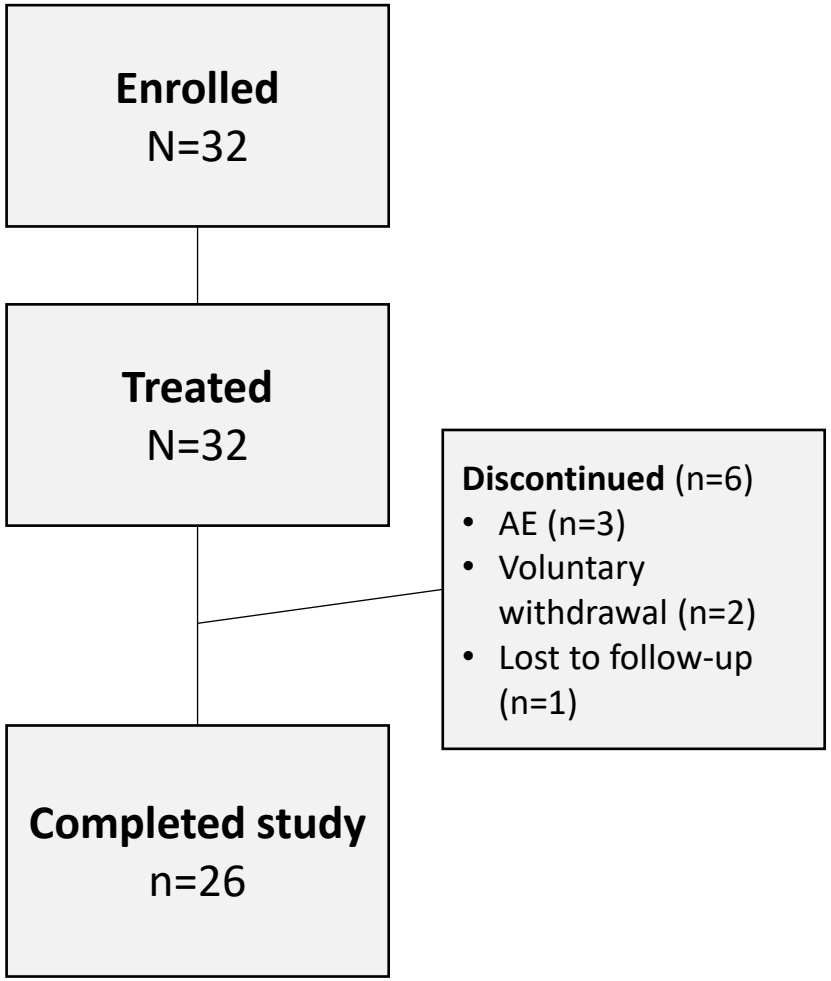
- Proportion of all participants achieving ≥10% weight loss
- Mean percent change from baseline in body weight in participants ≥12 years old
- Proportion of participants ≥12 years old achieving ≥25% improvement in weekly average of the daily hunger score
- Mean percent change from baseline in weekly average daily hunger score in participants ≥12 years old

Additional secondary endpoints Week 14[a]

- Mean percent change in body weight with setmelanotide vs placebo in participants ≥12 years old
- Mean percent change in weekly average daily hunger score in participants ≥12 years old with setmelanotide vs placebo

[a]Includes key Week-14 endpoints contained in this presentation.

Disposition and Baseline Demographics of Patients With BBS



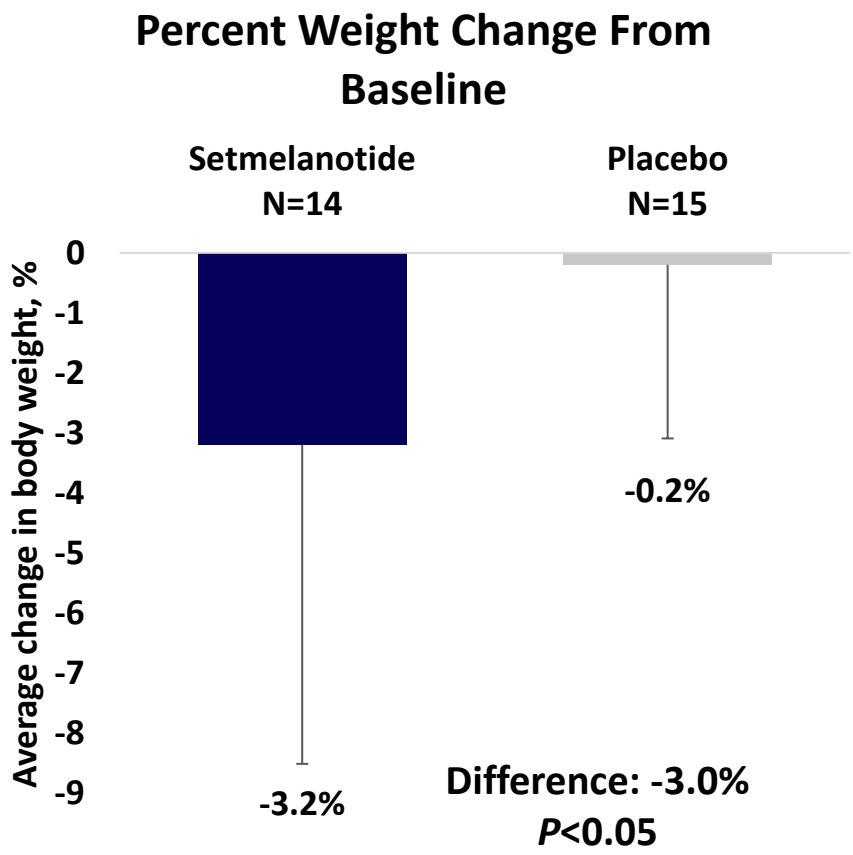
Baseline characteristics	Setmelanotide (N=16)	Placebo (N=16)	Total (N=32)
Age, years			
Mean (SD)	19.1 (9.8)	21.2 (10.7)	**20.2 (10.2)**
Range	7–42	10–44	**7–44**
Age group, n (%)			
≥12 years	14 (87.5)	15 (93.8)	**29 (90.6)**
Sex, n (%)			
Female	9 (56.3)	6 (37.5)	**15 (46.9)**
Male	7 (43.8)	10 (62.5)	**17 (53.1)**
Cognitively impaired, n (%)			
Yes	10 (62.5)	7 (43.8)	**17 (53.1)**
No	6 (37.5)	9 (56.3)	**15 (46.9)**
Weight, kg			
Mean (SD)	113.4 (30.1)	111.2 (26.4)	**112.3 (27.9)**
Range	49.3–173.8	70.7–166.0	**49.3–173.8**
BMI, kg/m^2			
Mean (SD)	41.7 (9.7)	41.6 (8.5)	**41.6 (9.0)**
Range	24.4–61.3	28.6–58.1	**24.4–61.3**

AE, adverse event; BBS, Bardet-Biedl syndrome; SD, standard deviation.

Setmelanotide Led to Significant Weight Loss Compared With Placebo in Participants Age ≥12 Years With BBS

At Week 14, participants with BBS age ≥12 years treated with setmelanotide lost an average of **–3.8 kg (–3.0%)** more than participants in the placebo group

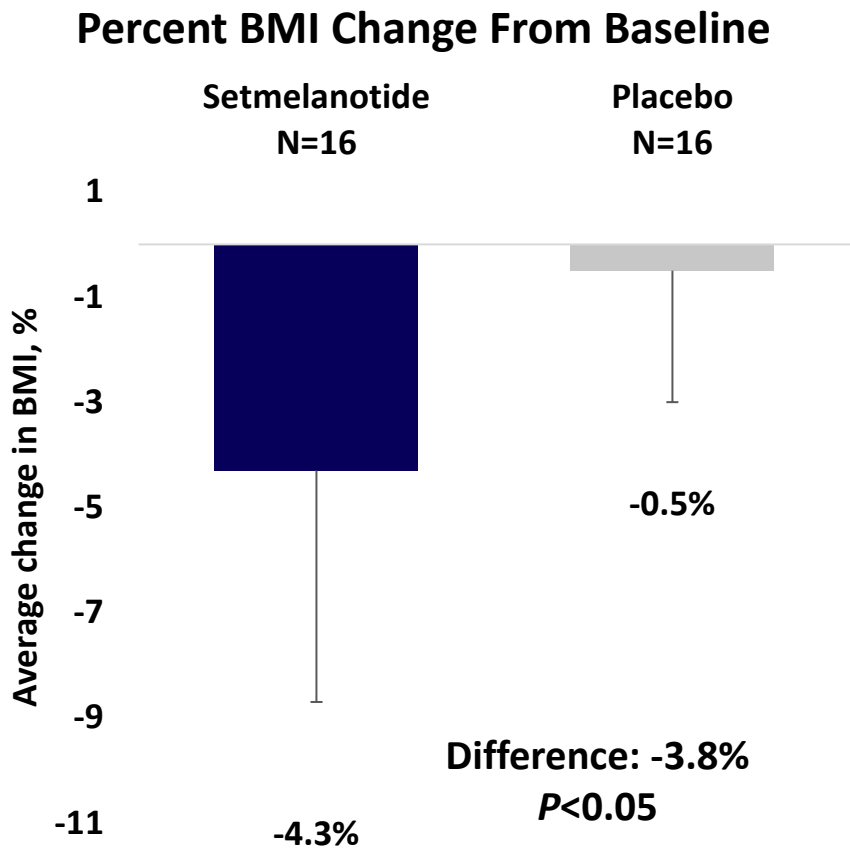
(*P*<0.05)



Data on this slide as of April 16, 2021. Error bars represent the standard deviation.
BBS, Bardet-Biedl syndrome.

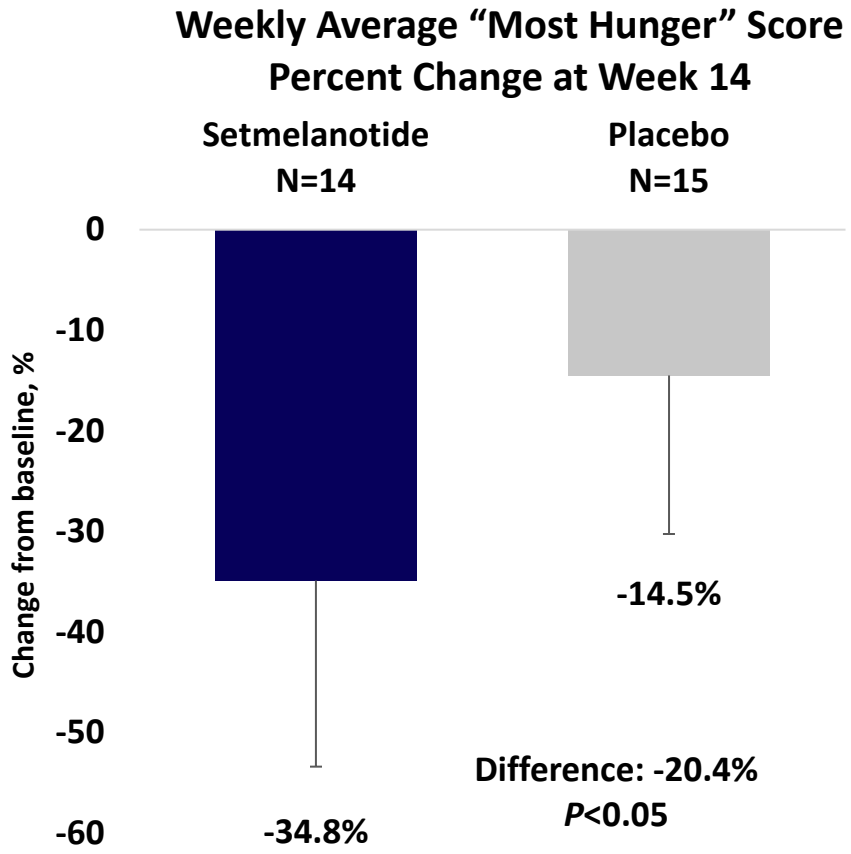
BMI at Week 14 Was Significantly Reduced With Setmelanotide Treatment Versus Placebo in Patients With BBS

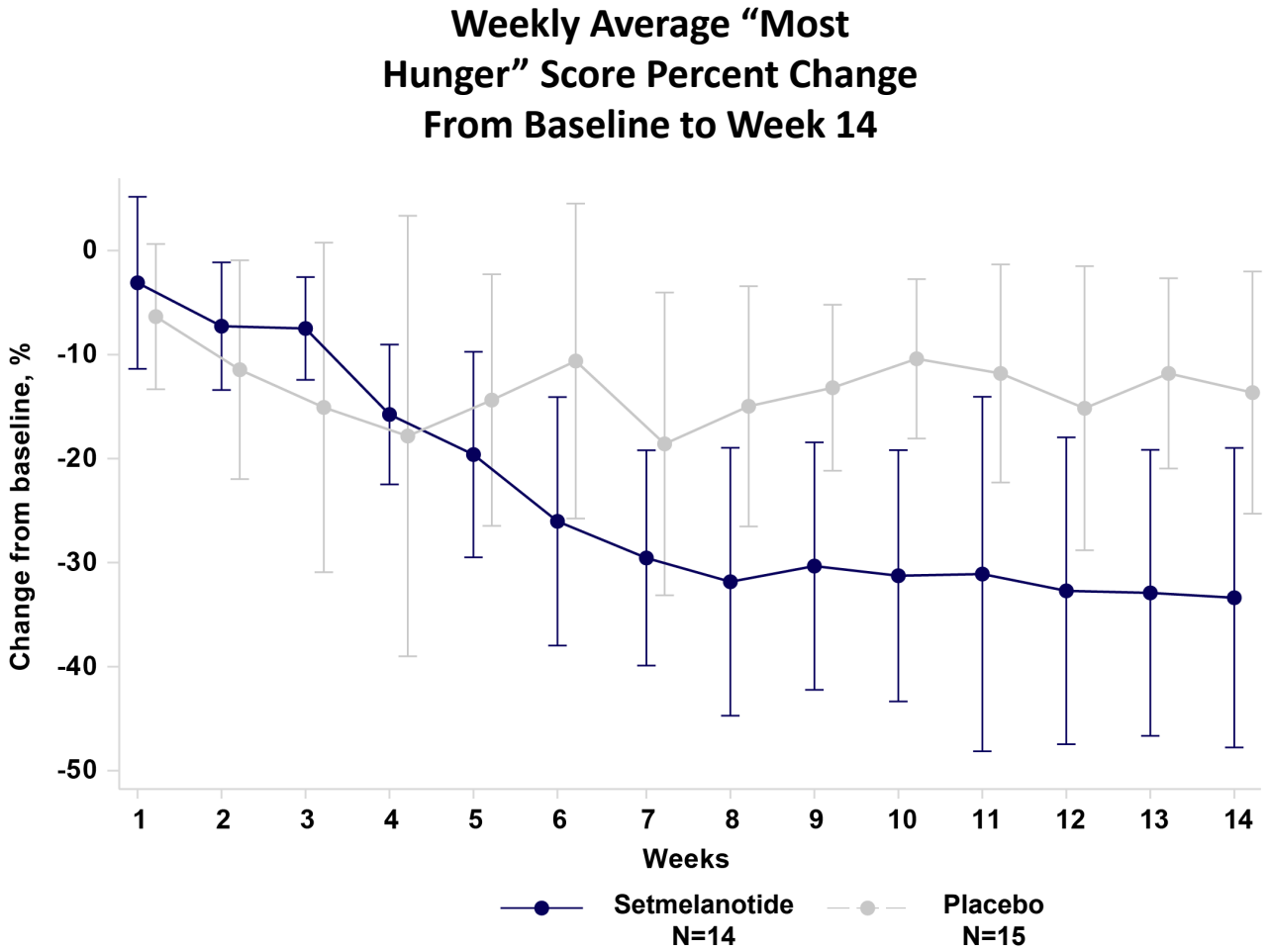
In all patients with BBS, those treated with setmelanotide achieved an average BMI reduction of **–1.5 kg/m² (–3.8%)** more at Week 14 compared with the participants receiving placebo (*P*<0.05)



Data on this slide as of April 16, 2021. Error bars represent the standard deviation.
BBS, Bardet-Biedl syndrome; BMI, body mass index.

Setmelanotide Treatment Led to Reduced Hunger With 14 Weeks of Treatment in Participants ≥12 Years With BBS Compared With Placebo





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BBS, Bardet-Biedl syndrome.

Rates of Common AEs Were Generally Similar Between Setmelanotide and Placebo During the Double-Blind Period

AEs occurring in the double-blind period, n (%)	Setmelanotide N=16	Placebo N=16	Total N=32
Treatment-emergent AEs occurring in ≥15% of participants			
Injection site erythema	8 (50.0)	7 (43.8)	15 (46.9)
Injection site pruritus	5 (31.3)	5 (31.3)	10 (31.3)
Injection site bruising	3 (18.8)	6 (37.5)	9 (28.1)
Skin hyperpigmentation	**9 (56.3)**	**0**	**9 (28.1)**
Injection site pain	3 (18.8)	5 (31.3)	8 (25.0)
Nausea	3 (18.8)	5 (31.3)	8 (25.0)
Injection site induration	4 (25.0)	2 (12.5)	6 (18.8)
Headache	0	4 (25.0)	4 (12.5)
Vomiting	3 (18.8)	0	3 (9.4)
HDL decrease	3 (18.8)	0	3 (9.4)
Nasal congestion	3 (18.8)	0	3 (9.4)

Data on this slide as of April 16, 2021.
AE, adverse event; HDL, high-density lipoprotein.

Setmelanotide Was Generally Well Tolerated in Patients With BBS During the 14-Week Double-Blind Period

AEs, n (%)	Setmelanotide N=16	Placebo N=16	Total N=32
Treatment-related AEs	14 (87.5)	14 (87.5)	28 (87.5)
Serious AEs	0	2 (12.5)	2 (6.3)
Serious treatment-related AEs	0	1 (6.3)	1 (3.1)
AEs leading to drug discontinuation	0	2 (12.5)	2 (6.3)
AEs leading to death	0	0	0

- 1 participant with BBS had a serious AE of anaphylaxis that was considered related to the treatment; the individual discontinued from therapy
- The participant was on placebo at the time of the reaction

Data on this slide as of April 16, 2021.
AE, adverse event; BBS, Bardet-Biedl syndrome.

Summary and Conclusions

- Overall, participants with BBS lost on average 3.2% of their body weight from baseline at Week 14, compared with negligible weight loss with placebo
- Setmelanotide significantly reduced “most hunger” compared with placebo at Week 14 in participants with BBS
- Setmelanotide was generally well tolerated, and the AE profile was consistent with what has been previously described
- Setmelanotide may be a viable treatment option for some participants with obesity due to BBS
  - Future analysis characterizing setmelanotide treatment nonresponders versus responders is planned

AE, adverse event; BBS, Bardet-Biedl syndrome.