Efficacy and Safety of Open-Label Setmelanotide in Bardet-Biedl Syndrome: a Phase 3 Trial

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Disclosures

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- GAM-M reports participation in advisory boards for Rhythm Pharmaceuticals, Inc.
- WKC reports research funding and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Rhythm Pharmaceuticals, Inc.
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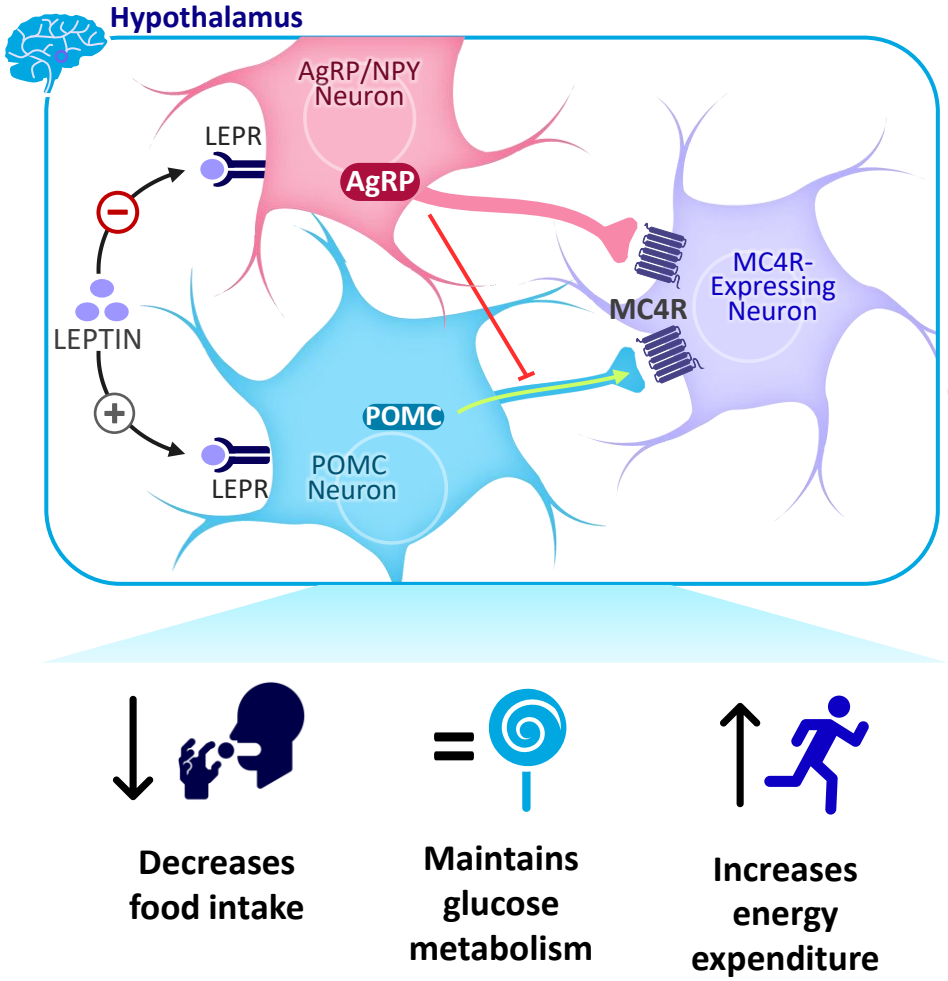
BBS and Energy Regulation

- BBS is a rare autosomal pleiotropic and multigenic syndrome involving primary cilia dysfunction[1-3]
- Patients 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 patients with BBS may be associated with reduced activation of the MC4R, although the molecular mechanisms are not fully understood[3,5]

Role of POMC neuron activation in metabolism[6-8]

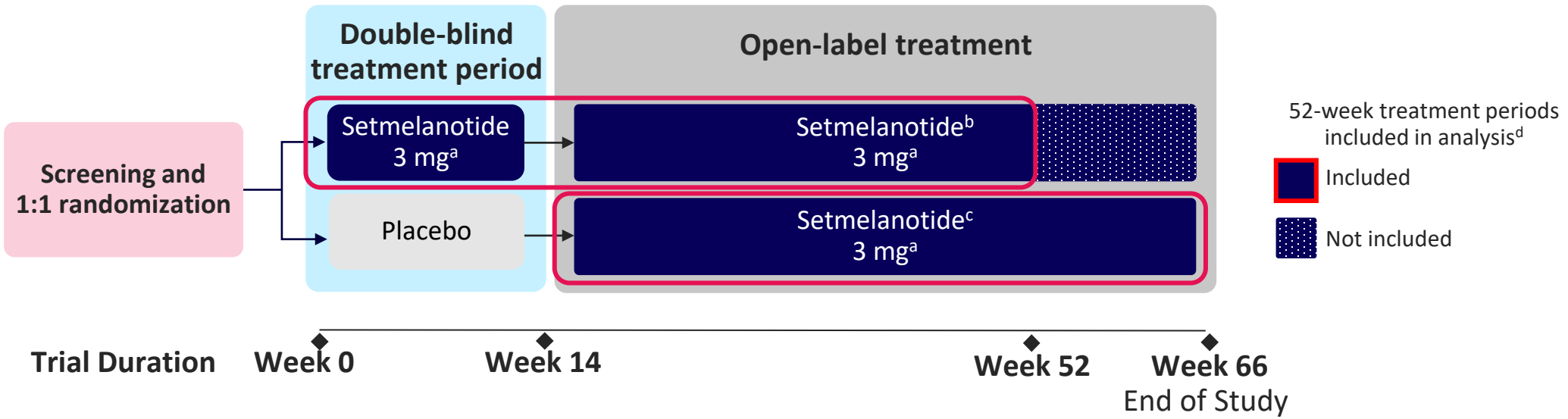


AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; NPY, neuropeptide Y; POMC, proopiomelanocortin.

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.** Farooqi et al. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **7.** Quarta et al. *Nat Metab.* 2021;3:299-308. **8.** Yazdi et al. *PeerJ*. 2015;3:e856.

Phase 3 Trial (NCT03746522) to Evaluate Setmelanotide in Patients With BBS

No specific guidance on diet and exercise given during the trial



Key inclusion criteria[1]

- Clinical diagnosis of BBS or Alström syndrome
- ≥6 years of age
- Obesity
  - ≥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 patients who received >52 weeks of setmelanotide at the end of study, analysis was performed for 52 weeks of setmelanotide. [c]A multiple imputation model was used to impute data in patients who received <52 weeks of setmelanotide at the time of the analysis. [d]Efficacy outcomes were assessed at 52 weeks on active treatment for each study group (ie, Week 0 to 52 for the setmelanotide group and Week 14 to 66 for the group assigned to placebo during the double-blind treatment period).

BBS, Bardet-Biedl syndrome; BMI, body mass index.

1. Haws et al. *Contemp Clin Trials Commun*. 2021;22:100780.

All Predefined Phase 3 Trial Endpoints Were Achieved

Primary endpoint at 52 weeks on active treatment

- Proportion of patients with BBS and Alström syndrome ≥12 years old achieving ≥10% weight loss

Key secondary endpoints at 52 weeks on active treatment

- Proportion of all patients with BBS and Alström syndrome achieving ≥10% weight loss
- Mean percent change from baseline in body weight in patients with BBS and Alström syndrome ≥12 years old
- Proportion of patients with BBS and Alström syndrome ≥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 patients with BBS and Alström syndrome ≥12 years old

Results from primary and key secondary endpoints were previously presented[1]

Given that all patients who met the primary endpoint were patients with BBS, this presentation reports updated results from patients with BBS

BBS, Bardet-Biedl syndrome.

1. Haws et al. Poster presented at: Pediatric Endocrine Society Annual Meeting; April 30-May 3, 2021; Virtual.

This Presentation Reports Updated Results From a Phase 3 Trial of Setmelanotide in Patients With BBS

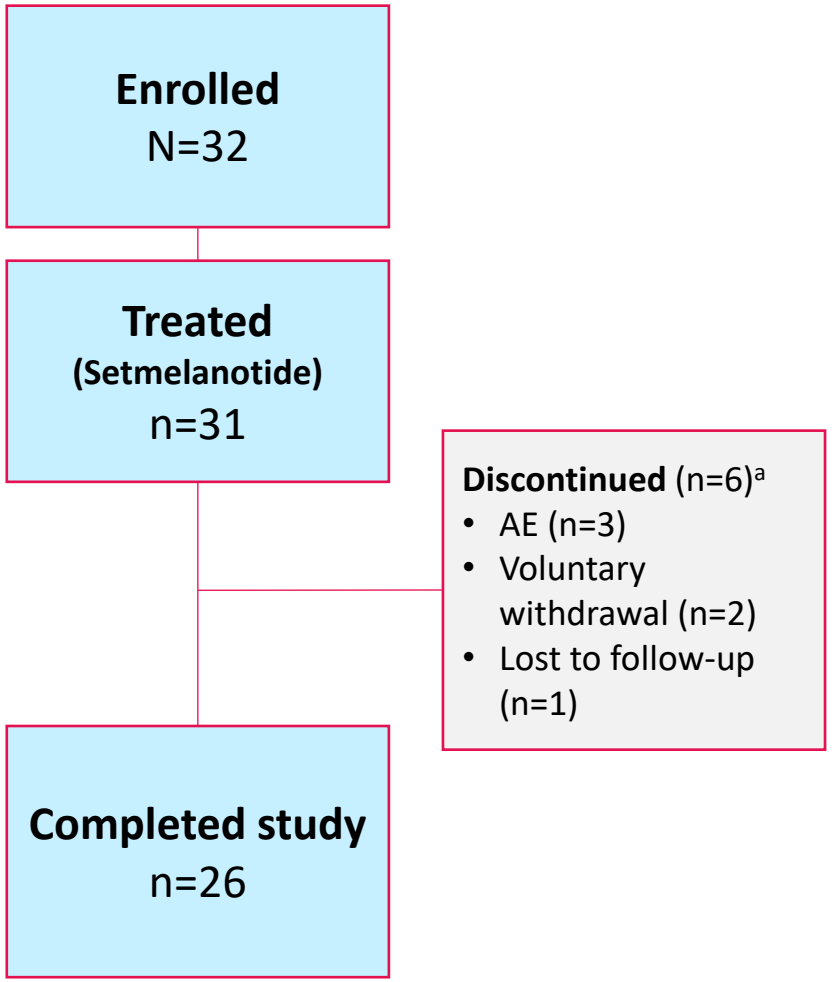
	Exploratory and ad hoc analyses at 52 weeks on active treatment

Disease subgroup analyses	• Patients with BBS
	  • Efficacy (listed below)
	  • Safety (frequency of AEs; all ages)

Age subgroups analyses	• Weight and BMI are reported separately for patients ≥18 years old and <18 years old
	  • BMI for patients ≥18 years old and <18 years old
	  • Body weight change for patients ≥18 years old
	  • BMI Z score for patients <18 years old; accounts for natural linear growth
	• Hunger is reported for patients ≥12 years old without cognitive impairment based on the assessment tool

AE, adverse event; BBS, Bardet-Biedl syndrome; BMI, body mass index.

Disposition and Baseline Demographics of Patients With BBS



[a]1 patient who received placebo discontinued during the placebo-controlled period and did not receive setmelanotide.
AE, adverse event; BBS, Bardet-Biedl syndrome; SD, standard deviation.

Baseline characteristics	Total (N=32)
Age, years	
Mean (SD)	**20.2 (10.2)**
Range	**7–44**
<16 years old, n	**15**
≥16 years old, n	**17**
Sex, n (%)	
Female	**17 (53.1)**
Male	**15 (46.9)**
Race, n (%)	
White	**28 (87.5)**
Black or African American	**1 (3.1)**
Other	**3 (9.4)**
Ethnicity, n (%)	
Hispanic or Latino	**1 (3.1)**
Not Hispanic or Latino	**31 (96.9)**
Weight, kg	
Mean (SD)	**112.3 (27.9)**
Range	**49.3–173.8**
BMI, kg/m^2	
Mean (SD)	**41.6 (9.0)**
Range	**24.4–61.3**

Setmelanotide Treatment Was Associated With Clinically Significant Reduction in BMI in Patients With BBS

–9.1% mean change in BMI in patients ≥18 years old

–9.5% mean change in BMI in patients <18 years old

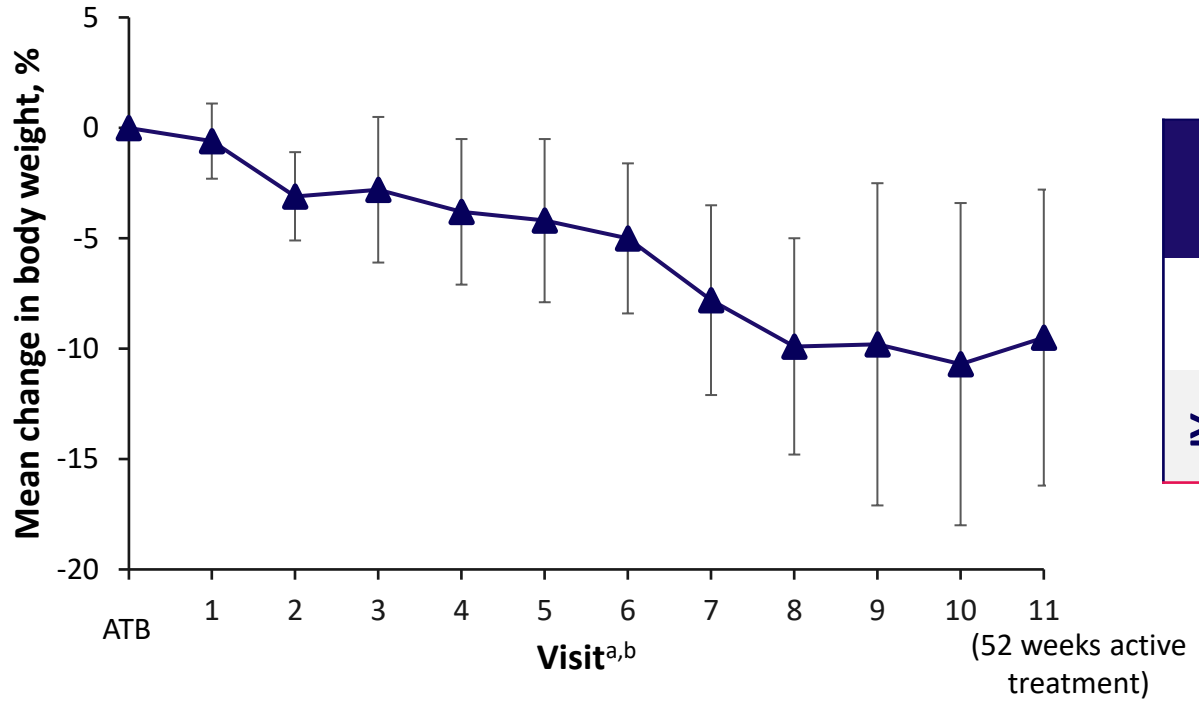
	Baseline	52 weeks on active treatment	Percent change from start of active treatment
Mean (SD) BMI in those ≥18 years old (n=15[a])	**46.4 kg/m²** (5.8)	**43.3 kg/m²** (7.2)	**–9.1** (6.8)
Mean (SD) BMI in those <18 years old (n=16[b])	**37.4 kg/m²** (9.4)	**34.2 kg/m²** (10.1)	**–9.5** (6.4)

[a]n=15 at baseline and 12 after 52 weeks on active treatment. [b]n=16 at baseline and 14 after 52 weeks on active treatment.
BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

Setmelanotide Treatment Was Associated With Clinically Significant Weight Loss in Patients With BBS ≥18 Years Old

–9.4 kg mean change in body weight after 52 weeks of setmelanotide treatment (SD, 9.4 kg [n=15]; *P*=0.0008)

–7.6% loss of body weight over the same time period (SD, 7.1%; *P*=0.0005)

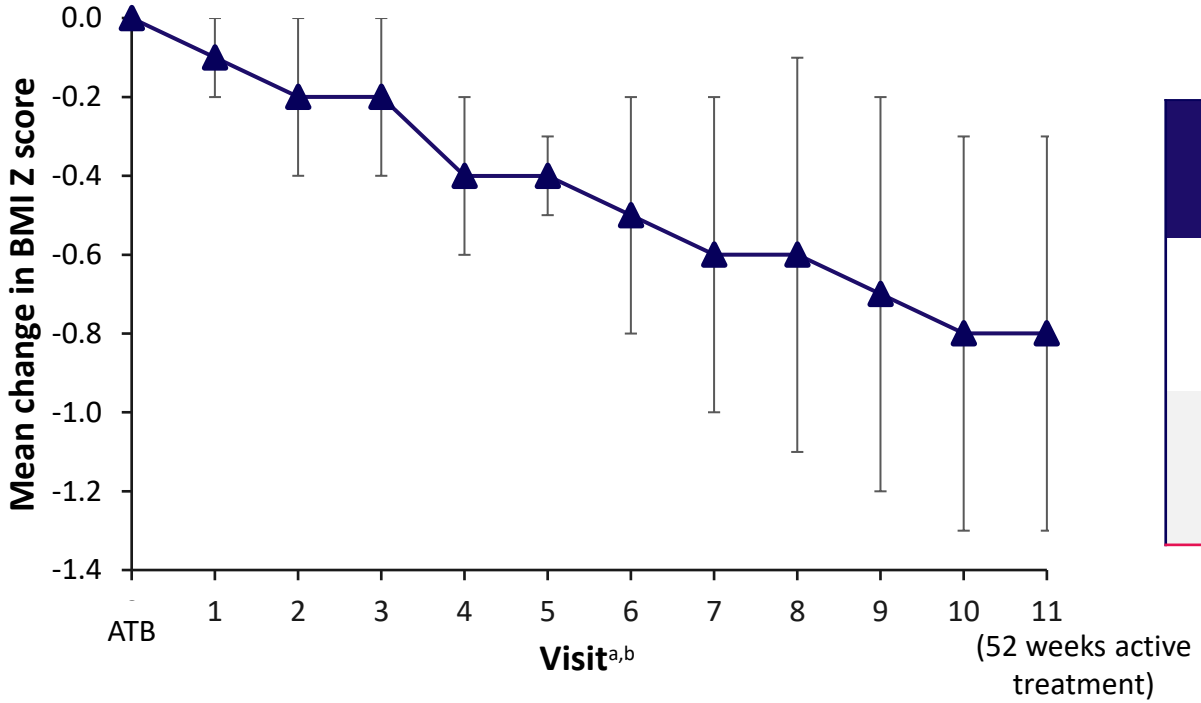


	52 weeks on active treatment
≥5% weight loss, n/N (%)	9/15 (60.0)
≥10% weight loss, n/N (%)	7/15 (46.7)

[a]Data shown by study visit do not include data imputed for patients who received <52 weeks of setmelanotide at the time of the analysis. [b]Populations sizes ranged from 7 to 15, with n=12 at 52 weeks on active treatment. Error bars are the standard deviation (SD).
ATB, active treatment baseline (defined as last measurement before the first dose of setmelanotide; ie, Week 0 for setmelanotide group and Week 14 for placebo group); BBS, Bardet-Biedl syndrome.

Setmelanotide Treatment Was Associated With Clinically Significant Reduction in BMI Z Score in Patients With BBS <18 Years Old

–0.75 points mean change in BMI Z score after 52 weeks of setmelanotide treatment (SD, 0.46 points [n=14])



	52 weeks on active treatment
≥0.2-point improvement in BMI Z score, n/N (%)	12/14 (85.7)
≥0.3-point improvement in BMI Z score, n/N (%)	10/14 (71.4)

[a]Data shown by study visit do not include data imputed for patients who received <52 weeks of setmelanotide at the time of the analysis. [b]Populations sizes ranged from 8 to 16, with n=14 at 52 weeks on active treatment. Error bars are the standard deviation (SD).
ATB, active treatment baseline (defined as last measurement before the first dose of setmelanotide; ie, Week 0 for setmelanotide group and Week 14 for placebo group); BBS, Bardet-Biedl syndrome; BMI, body mass index.

Setmelanotide Treatment Was Associated With Significant Reduction in Hunger in Patients With BBS ≥12 Years Old With No Cognitive Impairment

57.1% of patients with BBS ≥12 years old achieved a ≥25% reduction in maximal hunger score after 52 weeks of setmelanotide treatment (95% CI, 28.9%–82.3%; *P*<0.0001)

	Baseline	52 weeks on active treatment	Percent change from start of active treatment
Mean (SD) "most" hunger score (n=14)[a]	**7.0** (1.9)	**4.9** (2.5)	**–30.4** (26.5) ***P*=0.0004**

[a]Assessed using a numerical rating scale ranging from 0 to 10, where 0 = "not hungry at all" and 10 = "hungriest possible."
BBS, Bardet-Biedl syndrome; CI, confidence interval; SD, standard deviation.

Setmelanotide Was Generally Well Tolerated in Patients With BBS

	n (%)
Treatment-related AEs	32 (100.0)
Serious AEs	2 (6.3)
Serious treatment-related AEs	1 (3.1)
AEs leading to drug discontinuation	3 (9.4)
AEs leading to death	0

- 1 patient had a serious AE of anaphylaxis
  - Was considered related to treatment by the investigator; the patient was on placebo at the time of the AE
  - Patient discontinued from study treatment

	n (%)
Treatment-emergent AEs occurring in ≥15% of patients	
Skin hyperpigmentation	18 (56.3)
Injection site erythema	16 (50.0)
Nausea	11 (34.4)
Injection site pruritus	11 (34.4)
Injection site bruising	11 (34.4)
Injection site pain	10 (31.3)
Headache	9 (28.1)
Vomiting	9 (28.1)
Injection site induration	8 (25.0)
Diarrhea	7 (21.9)

Safety analysis set, defined as all patients who received ≥1 dose of study drug, reported.
AE, adverse event; BBS, Bardet-Biedl syndrome.

Summary and Conclusions

- In patients with obesity and BBS, setmelanotide was associated with significant weight loss in adults, BMI Z score improvements in children and adolescents, and hunger reduction
- Setmelanotide was generally well tolerated in patients with BBS, with no new safety concerns
- On the basis of these and earlier Phase 2 results,[1] setmelanotide may represent a novel treatment for hunger and obesity in patients with BBS
- Future analysis characterizing setmelanotide treatment in nonresponders versus responders is planned

BBS, Bardet-Biedl syndrome; BMI, body mass index.

1. Haws et al. *Diabetes Obes Metab.* 2020;22:2133-2140.