Efficacy and Safety of Setmelanotide in Patients Aged 2 to <6 Years With Rare Melanocortin-4 Receptor Pathway Diseases of Obesity: Results From VENTURE, a Phase 3, Multicenter, 1-Year, Open-Label Trial

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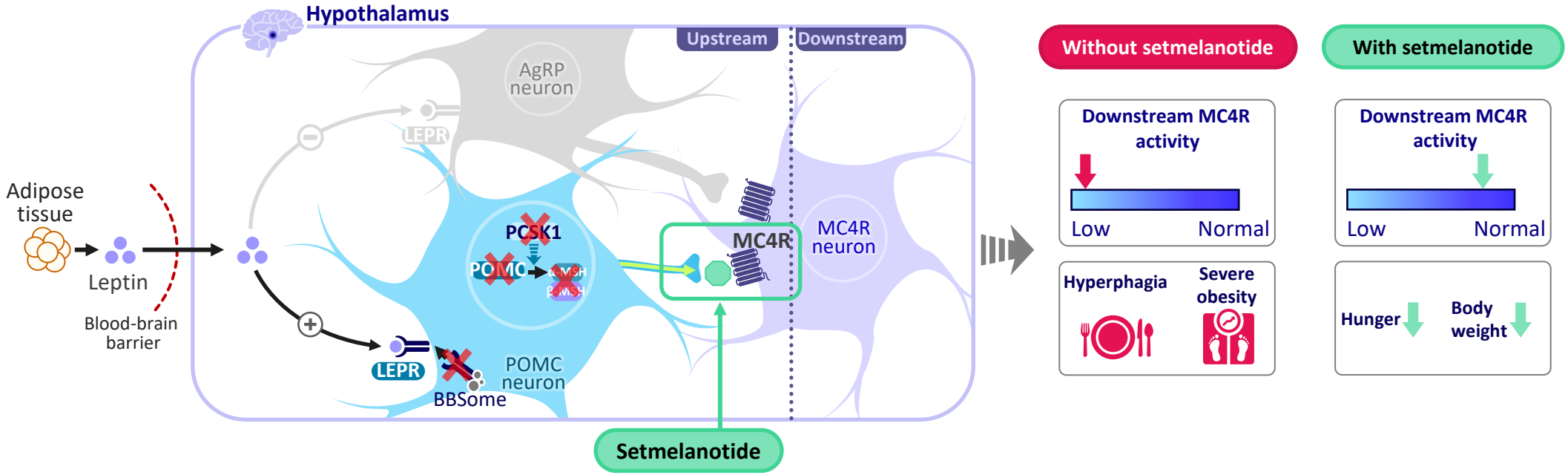
Pediatric Endocrine Society Annual Meeting ● May 2-5, 2024 ● Chicago, IL

Disclosures

- JA has received payment for lectures and advisory boards from Rhythm Pharmaceuticals, Inc.
- UO, CFV, IF, and MMK's institutions have received funding and materials for research from Rhythm Pharmaceuticals, Inc.
- SF has received speaker fees from Rhythm Pharmaceuticals, Inc.
- CC, CS, and GY are full-time employees of Rhythm Pharmaceuticals, Inc. and have received company-awarded stocks or stock options

Energy Balance Is Regulated by the Hypothalamic MC4R Pathway

- Under physiologic conditions, the MC4R pathway regulates hunger, satiety, energy expenditure, and body weight, whereas rare variants in genes involved in the MC4R pathway are associated with hyperphagia and early-onset, severe obesity[1-9]
- The MC4R agonist setmelanotide reduced BMI and hunger in Phase 3 trials of patients aged ≥6 years with POMC deficiency, LEPR deficiency, or BBS[10,11]
- There are currently no approved therapies for those aged <6 years in these patient populations[12]



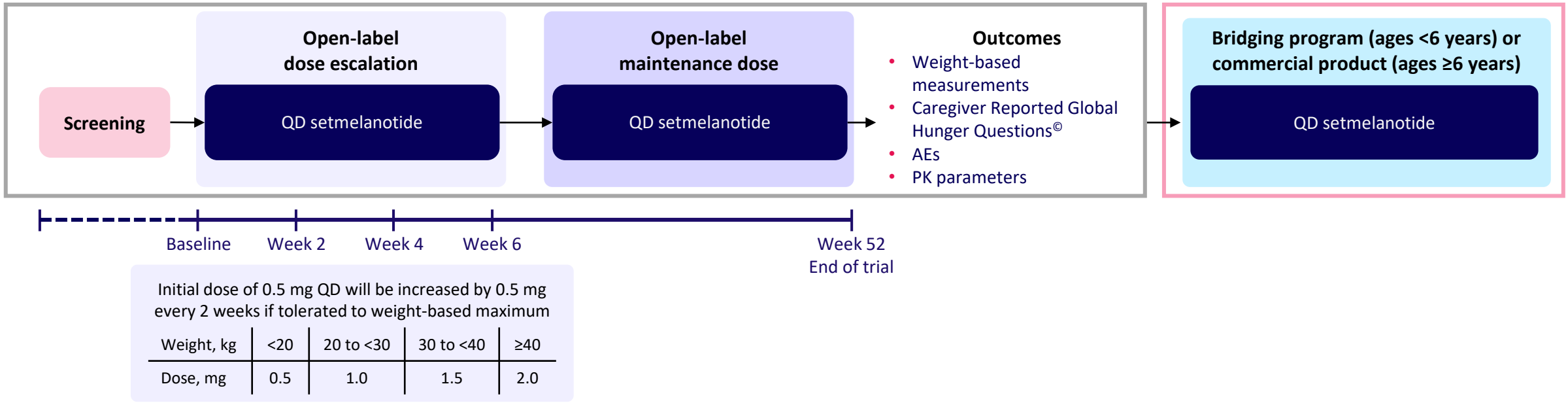
Objective: to present primary results from VENTURE (NCT04966741), a Phase 3, 1-year, open-label trial of setmelanotide in patients aged 2 to <6 years with POMC deficiency, LEPR deficiency, or BBS

AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; BBSome, complex of 8 Bardet-Biedl syndrome proteins; BMI, body mass index; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **2.** Yazdi et al. *PeerJ*. 2015;3:e856. **3.** Farooqi, O'Rahilly. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **4.** Guo, Rahmouni. *Trends Endocrinol Metab*. 2011;22:286-293. **5.** Guo et al. *PLoS Genet*. 2016;12:e1005890. **6.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **7.** Seo et al. *Hum Mol Genet*. 2009;18:1323-1331. **8.** Sherafat-Kazemzadeh et al. *Pediatr Obes*. 2013;8:e64-e67. **9.** Vaisse et al. *Cold Spring Harb Perspect Biol*. 2017;9:a028217. **10.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **11.** Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10:859-868. **12.** Dubern et al. *JCEM Case Rep*. 2023;1:luad041.

Study Design and Eligibility Criteria

- Study design (NCT04966741)



Initial dose of 0.5 mg QD will be increased by 0.5 mg every 2 weeks if tolerated to weight-based maximum

Weight, kg	<20	20 to <30	30 to <40	≥40
Dose, mg	0.5	1.0	1.5	2.0

Inclusion criteria

- Patients aged 2 to <6 years with hyperphagia and obesity due to biallelic *POMC* or *PCSK1* variants (POMC deficiency), biallelic *LEPR* variants (LEPR deficiency), or genetically confirmed BBS

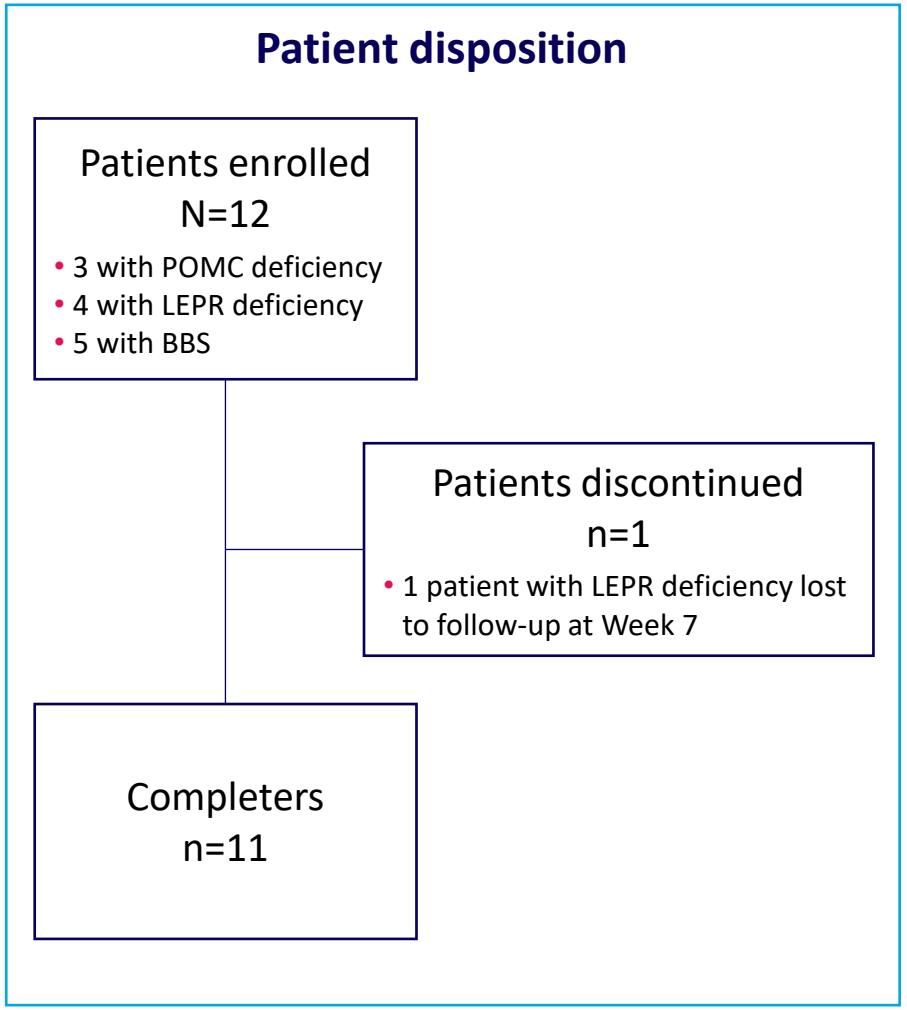
Key exclusion criteria

- Significant dermatologic findings (eg, melanoma, skin lesions)
- HbA_{1c} >9.0% at screening
- GFR <60 mL/min/1.73 m^2
- Considered not suitable to participate by Investigator
- Participation in any clinical trial with an investigational drug/device within 3 months prior to the first day of dosing
- History of significant liver disease (other than NAFLD or NASH) or abnormal hepatic function

AE, adverse event; BBS, Bardet-Biedl syndrome; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; LEPR, leptin receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetics; POMC, proopiomelanocortin; QD, once daily

Baseline Characteristics and Disposition

Parameter	POMC or LEPR deficiency	BBS	Total
Enrolled patients, n	7	5	12
Age range, years	3-4	2-5	2-5
Male, n (%)	5 (71.4)	2 (40.0)	7 (58.3)
Race, n (%)*			
White	3 (42.9)	4 (80.0)	7 (58.3)
Asian	-	1 (20.0)	1 (8.3)
Other	2 (28.6)	-	2 (16.7)
NR or unknown	2 (28.6)	-	2 (16.7)
Hispanic or Latino, n (%)	1 (14)	-	1 (8)
BMI, mean (SD), kg/m^2	34.5 (7.1)	23.7 (3.5)	29.9 (7.9)
BMI-Z score, mean (SD)			
CDC	5.0 (1.1)	3.1 (0.7)	4.1 (1.4)
WHO	10.8 (3.8)	4.2 (1.1)	8.0 (4.4)
%BMI$_{95}$, mean (SD)	191.1 (38.6)	128.8 (16.7)	165.1 (44.1)
Waist circumference, mean (SD), cm	89.0 (14.4)	66.2 (13.3)	79.5 (17.7)



*Patients who selected ≥1 race were counted once for each selection.

%BMI$_{95}$, percent of the 95th percentile for BMI; BBS, Bardet-Biedl syndrome; BMI, body mass index; CDC, Centers for Disease Control and Prevention; LEPR, leptin receptor; POMC, proopiomelanocortin; NR, not reported; SD, standard deviation; WHO, World Health Organization.

Coprimary Endpoints: From Baseline to Week 52 in Safety Population (Data as Observed)

The proportion of patients achieving a clinically meaningful decrease in BMI Z score (WHO) of ≥0.2

83.3% (10 of 12)*
95% CI, 58.7-99.8

- 85.7% of patients with POMC or LEPR deficiency
- 80.0% of patients with BBS

Mean percent change in absolute BMI

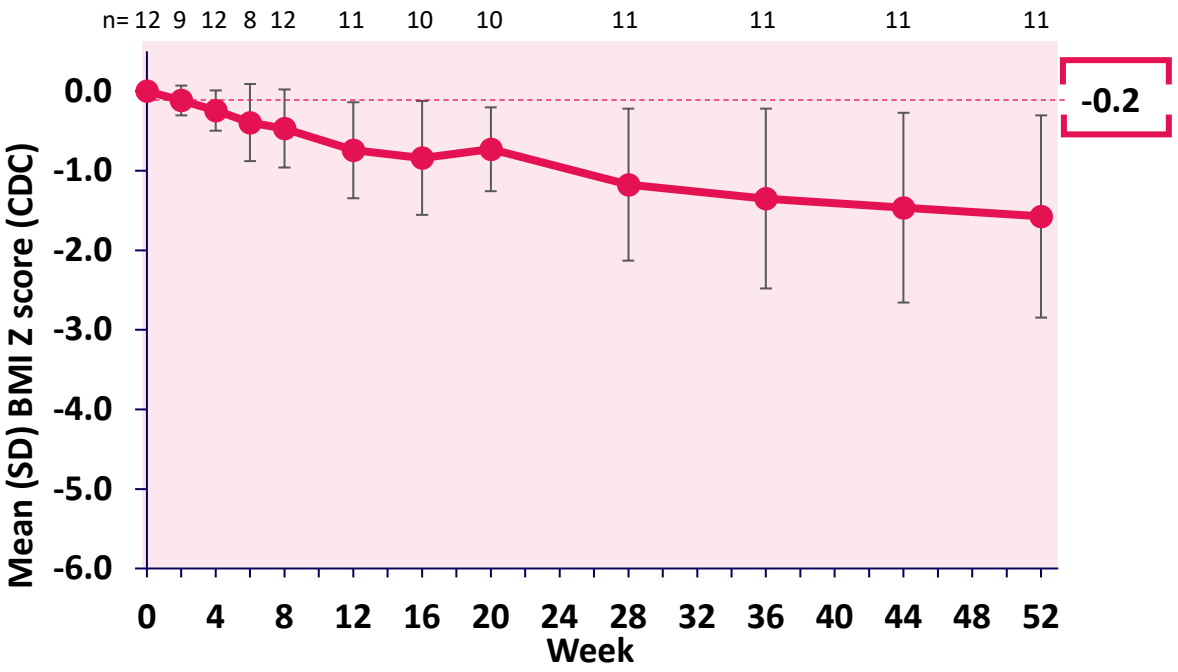
−18.4%

- −25.6% for patients with POMC or LEPR deficiency
- −9.7% for patients with BBS

*The same proportion of patients achieved a ≥0.2-point reduction in BMI Z score when calculated via the Centers for Disease Control and Prevention methodology.
BBS, Bardet-Biedl syndrome; BMI, body mass index; CI, confidence interval; LEPR, leptin receptor; POMC, proopiomelanocortin; WHO, World Health Organization.

Mean BMI Z Score Reduction in Safety Population (Data as Observed)

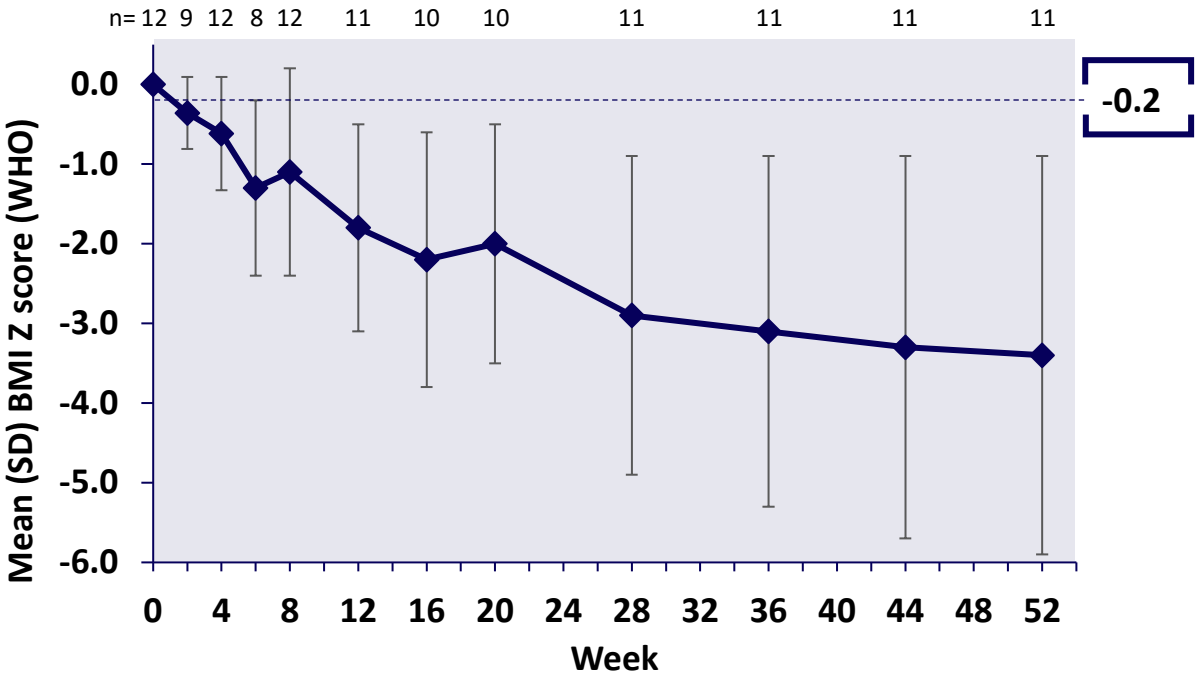
BMI-Z (CDC) change from baseline



Overall mean change from baseline to Week 52 (SD) **–1.6 (1.2)**

POMC/LEPR = –2.2 (1.2) **BBS = –0.8 (0.8)**

BMI-Z (WHO) change from baseline

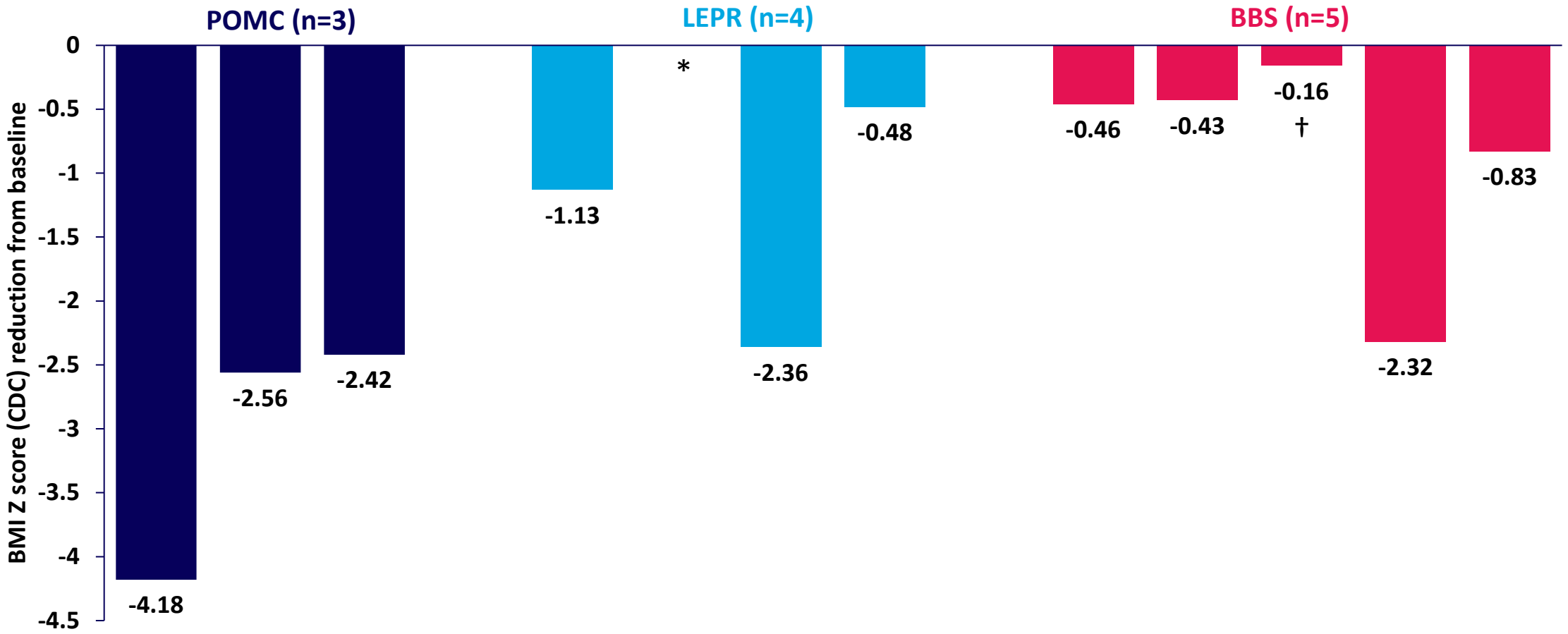


Overall mean change from baseline to Week 52 (SD) **–3.4 (2.5)**

POMC/LEPR = –5.2 (1.9) **BBS = –1.3 (1.2)**

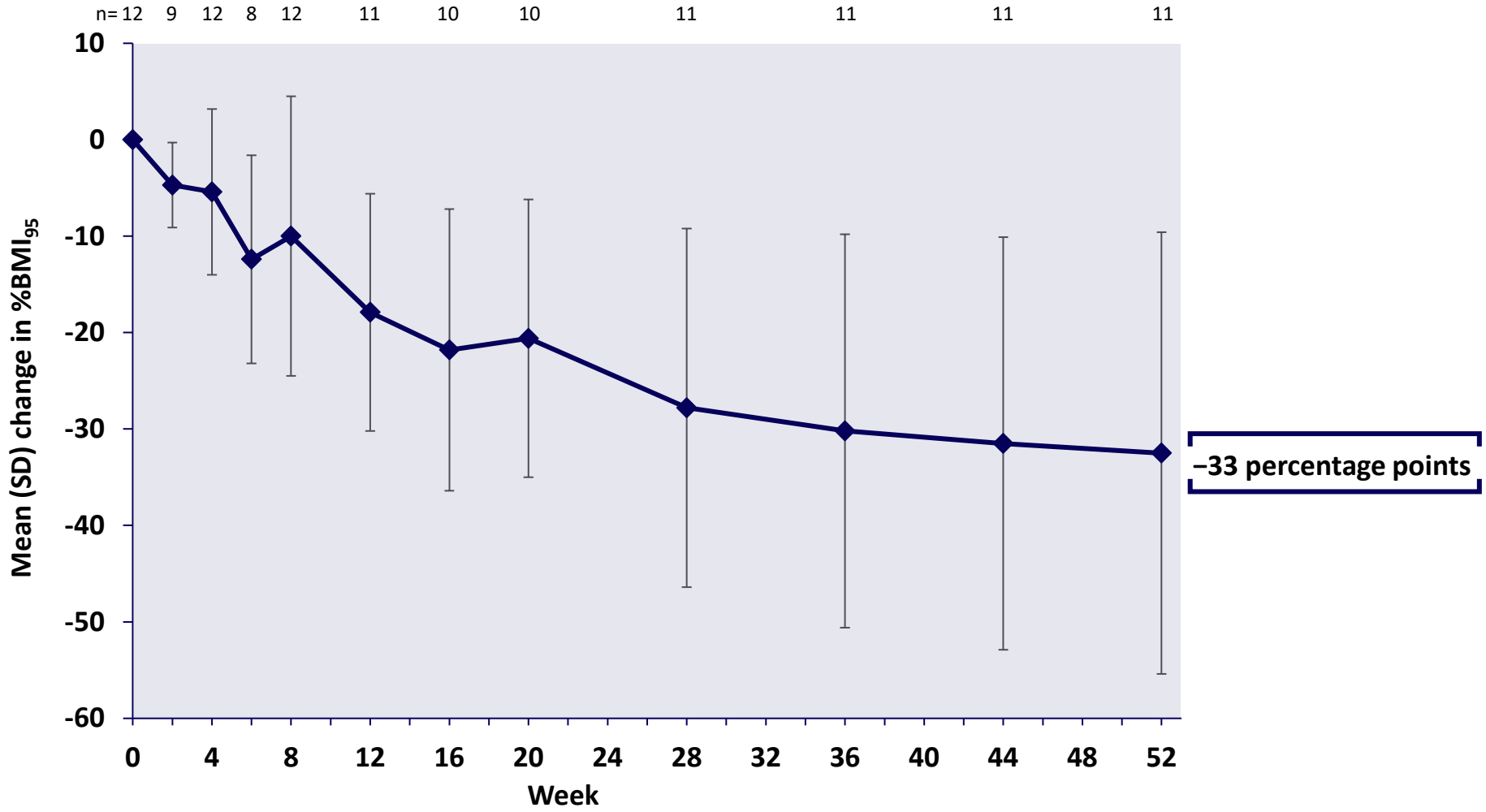
BBS, Bardet-Biedl syndrome; BMI, body mass index; CDC, Centers for Disease Control and Prevention; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation; WHO, World Health Organization.

Individual BMI Z Score (CDC) Reductions at Week 52 (Data as Observed)



*Patient was nonadherent and lost to follow-up prior to Week 52. †Patient was nonadherent.
BBS, Bardet-Biedl syndrome; BMI, body mass index; CDC, Centers for Disease Control and Prevention; LEPR, leptin receptor; POMC, proopiomelanocortin.

Change in %BMI_{95} From Baseline (Data as Observed)

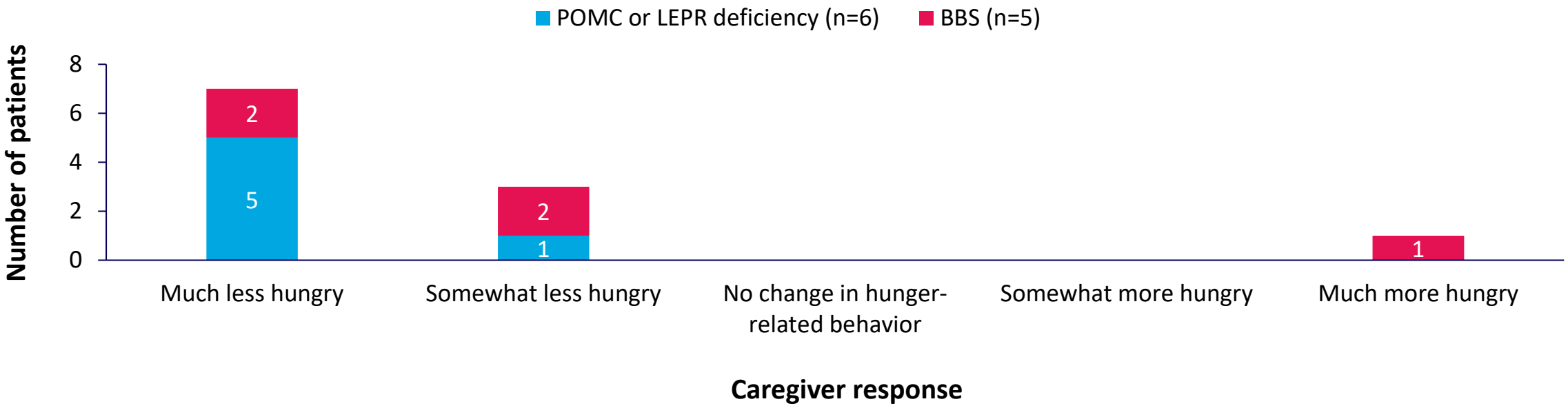


%BMI_{95}, percent of the 95th BMI percentile; SD, standard deviation.

Reduction in Patient Hunger Over 52 Weeks as Observed by Caregivers

- Overall, 10 of 11 patients (91%; 6 of 6 with POMC or LEPR deficiency; 4 of 5 with BBS) demonstrated hunger reduction at 52 weeks compared with before the study, as observed by caregivers

How hungry has your child acted in the past 7 days compared with before starting this study?



BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; POMC, proopiomelanocortin.

Adverse Events

- All patients had at ≥1 AE and ≥1 TRAE
  - All AEs were mild (7 patients [58.3%]) or moderate (5 patients [41.7%])
- There were no discontinuations related to AEs, serious AEs, or deaths
- There was no evidence of impaired growth or neurocognitive development due to setmelanotide

TRAEs in ≥15% of the total study cohort

TRAE, n (%)	POMC or LEPR deficiency (n=7)	BBS (n=5)	Total (N=12)
Skin hyperpigmentation	5 (71.4)	4 (80.0)	9 (75.0)
Injection site bruising	1 (14.3)	3 (60.0)	4 (33.3)
Injection site pruritus	1 (14.3)	3 (60.0)	4 (33.3)
Injection site discoloration	2 (28.6)	1 (20.0)	3 (25.0)
Injection site erythema	0 (0)	2 (40.0)	2 (16.7)
Vomiting	2 (28.6)	1 (20.0)	3 (25.0)
Abdominal pain	1 (14.3)	1 (20.0)	2 (16.7)
Melanocytic nevus	3 (42.9)	1 (20.0)	4 (33.3)
Polydipsia	1 (14.3)	1 (20.0)	2 (16.7)

AE, adverse event; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; POMC, proopiomelanocortin; TRAE, treatment-related AE.

Conclusions

- Setmelanotide was well tolerated and demonstrated consistent, clinically meaningful weight-related reductions in patients 2 to <6 years of age

Clinically meaningful reductions in BMI and BMI Z score (CDC and WHO)

Most caregivers reported a reduction in patient hunger at 52 weeks

Generally well tolerated with a safety profile similar to that seen in older patients

BMI, body mass index; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.