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Long-term weight outcomes of setmelanotide in paediatric participants with Bardet-Biedl syndrome or with POMC or LEPR deficiency and obesity

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Disclosures

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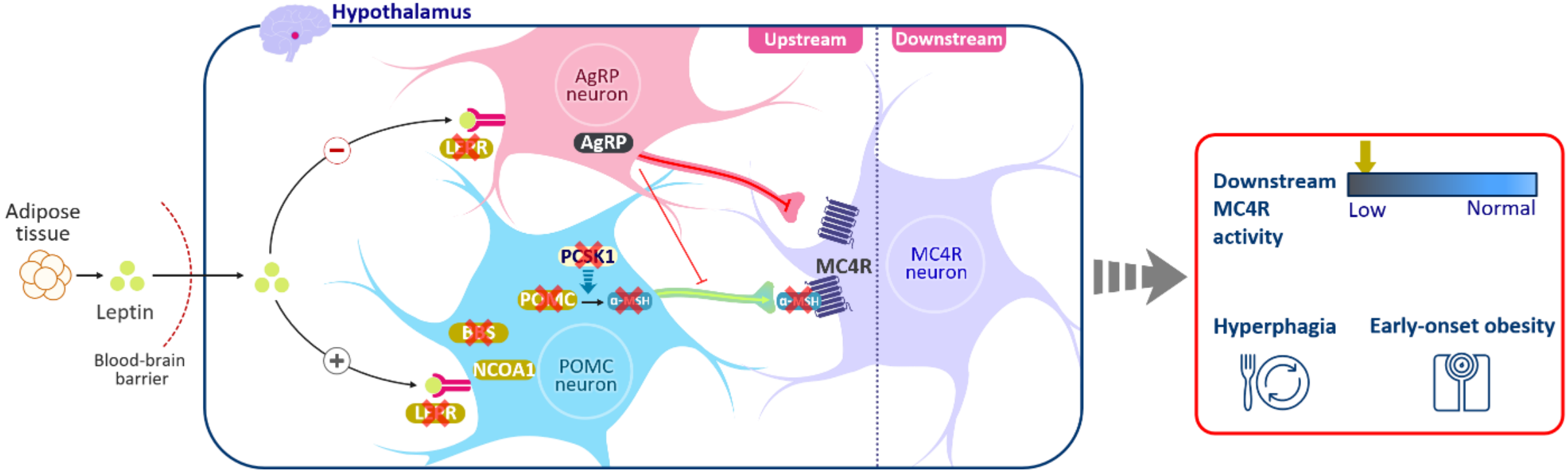
Introduction

- The melanocortin-4 receptor (MC4R) pathway controls hunger, satiety, and energy expenditure, which in turn regulates body weight[1,2]
- Impaired MC4R pathway signalling in patients with Bardet-Biedl syndrome (BBS), proopiomelanocortin (POMC) deficiency, or leptin receptor (LEPR) deficiency can cause hyperphagia (pathological, insatiable hunger) and early-onset obesity that has historically been resistant to medical treatment[3-10]



AgRP, agouti-related peptide; Bardet-Biedl syndrome; α-MSH, alpha melanocyte-stimulating hormone; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.
1. Kühnen et al. *Trends Mol Med.* 2019;25(2):136-148. **2.** Sohn et al. *Cell.* 2013;152(3):612-9. **3.** Krude et al. *Nat Genet*. 1998;19(2):155–157. **4.** Seo et al. *Hum Mol Genet*. 2009;18(7):1323-1331. **5.** Forsythe et al. *Front Pediatr.* 2018;6:23. **6.** Abuzzahab MJ et al. *Obesity (Silver Spring).* 2025;33(7):1217–1231. **7.** Farooqi et al. *Diabetes*. 2006;55(9):2549-25537. **8.** Folon et al. *Lancet Diabetes Endocrinol*. 2023;11(3):182-190. **9.** Montague et al. *Nature*. 1997;387:903-908. **10**. Clément et al. *Nature*. 1998;26;392(6674):398-401.

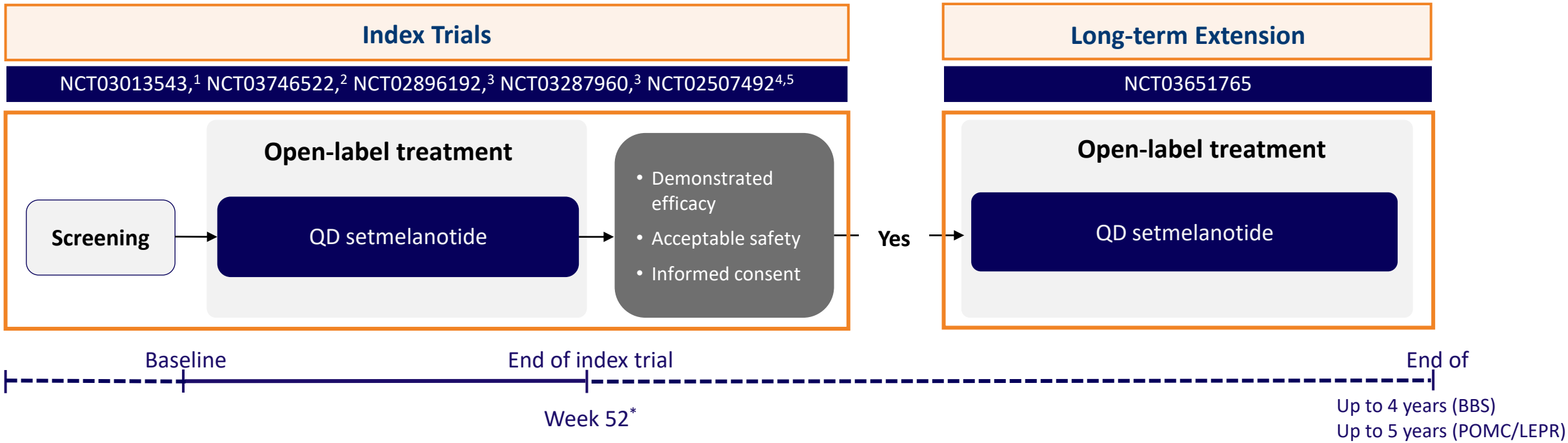
Study rationale and objectives

- In separate 1-year pivotal Phase 3 clinical trials in adult and paediatric participants with BBS or POMC/LEPR deficiency, treatment with the MC4R agonist setmelanotide was associated with clinically meaningful improvements in weight and hunger-related outcomes, with no new safety concerns[1,2,3]
- Setmelanotide has been approved by the EMA for the treatment of certain rare MC4R pathway diseases, including BBS and POMC/LEPR deficiency, and aHO for the treatment of obesity and the control of hunger[4]

Objective: To report long-term efficacy and safety outcomes over 4 and 5 years of setmelanotide treatment in paediatric participants (<18 years old) with BBS and POMC/LEPR deficiency, respectively

aHO, hypothalamic obesity; BBS, Bardet-Biedl syndrome; EMA, European Medicines Agency; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin. **1.** Haqq et al. *Lancet Diabetes Endocrinol.* 2022;10(12):859-868. **2.** Haws et al. *Diabetes Obes Metab.* 2020;22(11):2133-2140. **3.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **4**. European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/imcivree-epar-product-information_en.pdf.

Study design and outcomes

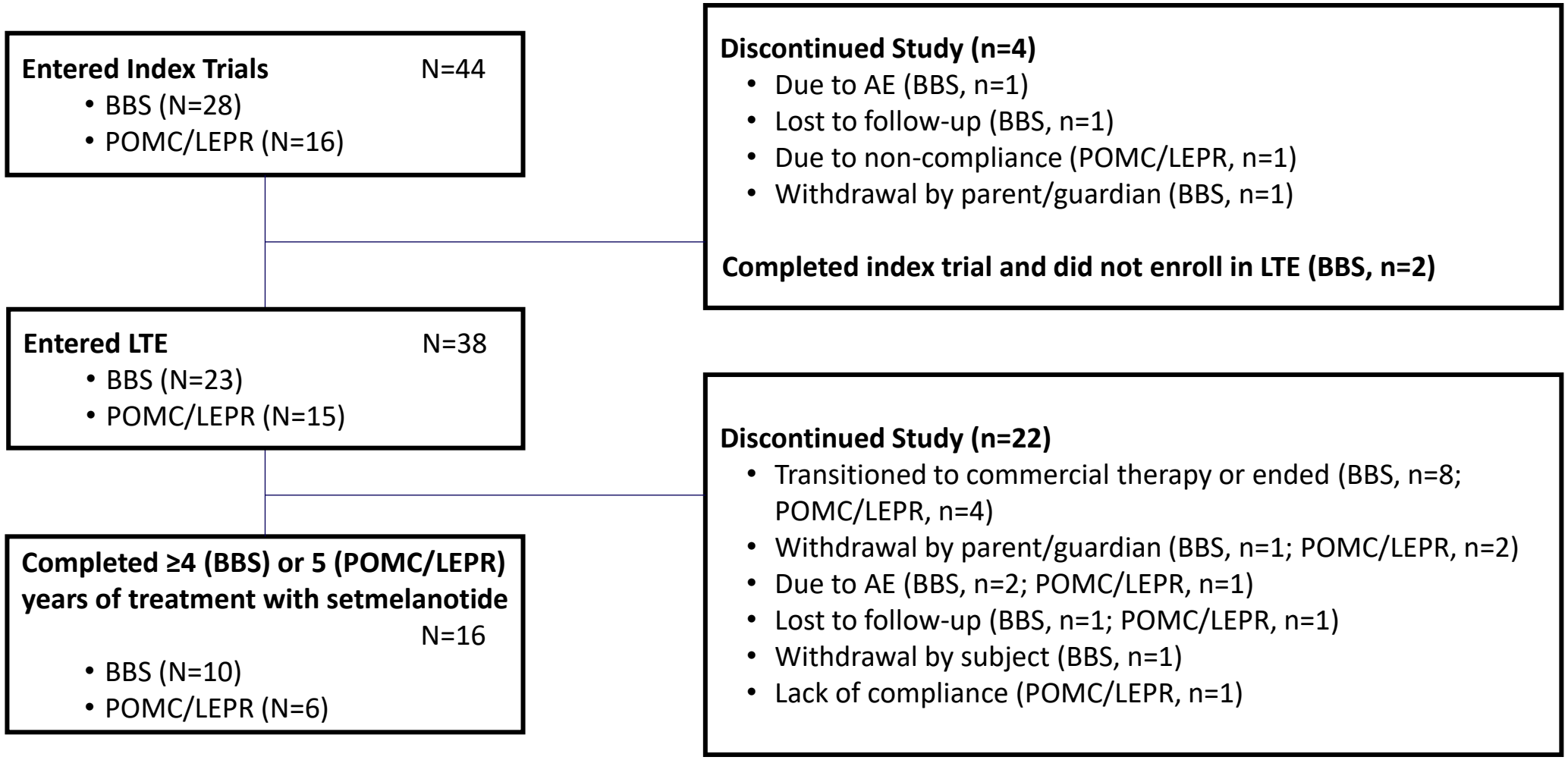


Eligibility and outcomes for paediatric participants (age <18 years)

Index trial eligibility:	Eligibility:	Outcomes:
• Participants with BBS, POMC or LEPR deficiency, and obesity†	• Index trial completion	• Change from baseline in weight parameters (BMI, BMI z-score)
• BMI ≥95th percentile for age (<18 years) and sex	• Adequate safety	• Long-term safety and tolerability
	• Clinically meaningful weight response from baseline with setmelanotide (reduction of ≥3% BMI or ≥0.2 BMI z-score)	

*Not all participants received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. †Exact eligibility criteria differ slightly across index trials. BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; , long-term extension; POMC, proopiomelanocortin; QD, once daily. **1.** Haws et al. *Diabetes Obes Metab.* 2020;22(11):2133-2140. **2.** Haqq et al. *Lancet Diabetes Endocrinol.* 2022;10(12):859-868. **3.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **4.** Kühnen et al. *N Engl J Med*. 2016;375:240-246. **5.** Clément et al. *Nat Med*. 2018;24:551-555.

Paediatric participant disposition



AE, adverse event; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin.

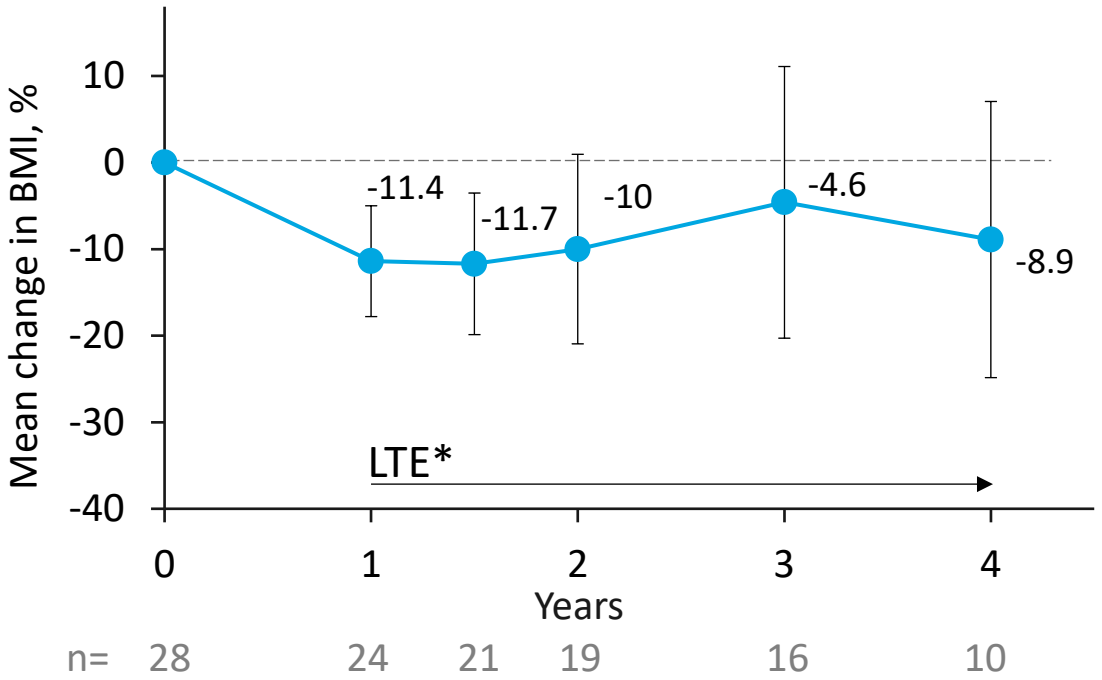
Baseline demographics and characteristics

	BBS N=28	POMC/LEPR N=16
Age, mean (SD; range), years	11.8 (3.21; 6-17)	12.8 (2.93; 7-17)
Sex, n (%)		
Male	12 (42.9)	9 (56.3)
Female	16 (57.1)	7 (43.8)
Race, n (%)		
White	23 (82.1)	10 (62.5)
Black or African American	3 (10.7)	0
Asian	1 (3.6)	0
Other	1 (3.6)	6 (37.5)
Ethnicity, n (%)		
Not Hispanic or Latino	26 (92.9)	14 (87.5)
Hispanic or Latino	1 (3.6)	1 (6.3)
Not reported/unknown	1 (3.6)	1 (6.3)
Weight, mean (SD), kg	95.0 (32.7)	97.3 (28.2)
BMI, mean (SD), kg/m^2	37.8 (8.9)	37.2 (7.1)
BMI z-score, mean (SD)*	4.26 (1.65)	3.86 (0.75)
Waist circumference, mean (SD), cm	106.1 (18.7)	107.7 (14.1)

*BMI z-score calculated according to the World Health Organization 2007 method.
BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

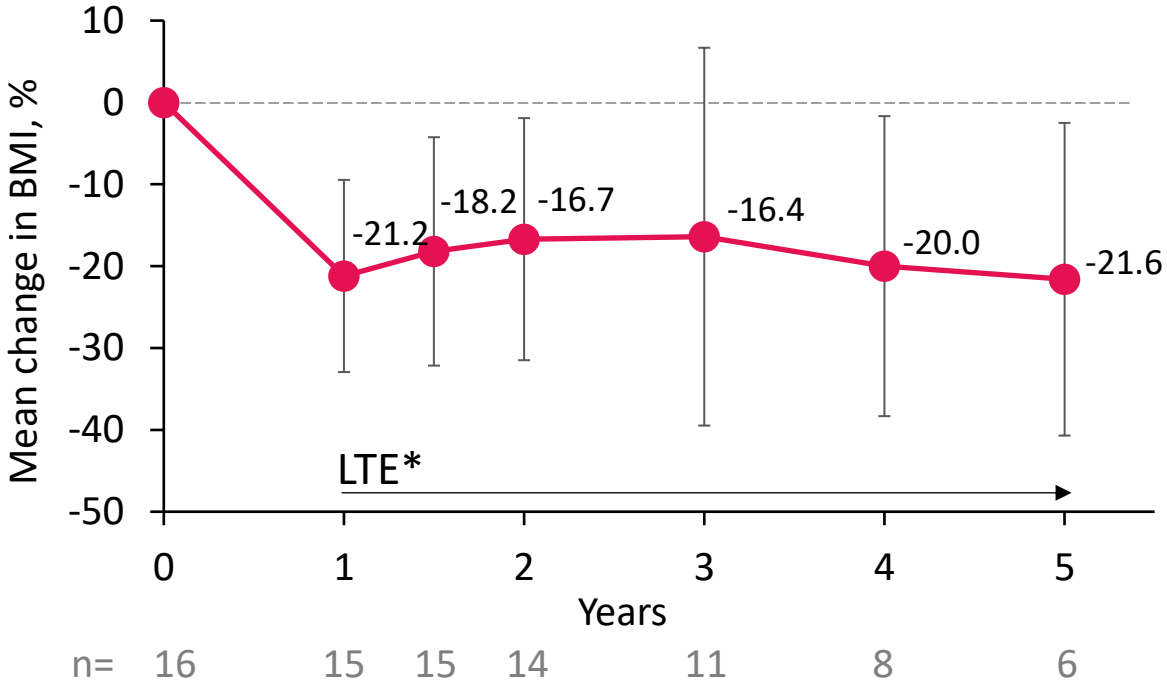
Setmelanotide treatment led to sustained reduction in BMI for paediatric participants with BBS or with POMC/LEPR deficiency

BBS



- In participants with BBS, the mean percent change from baseline in BMI was −8.9% (SD, 16.0) at Year 4 (n=10)

POMC/LEPR

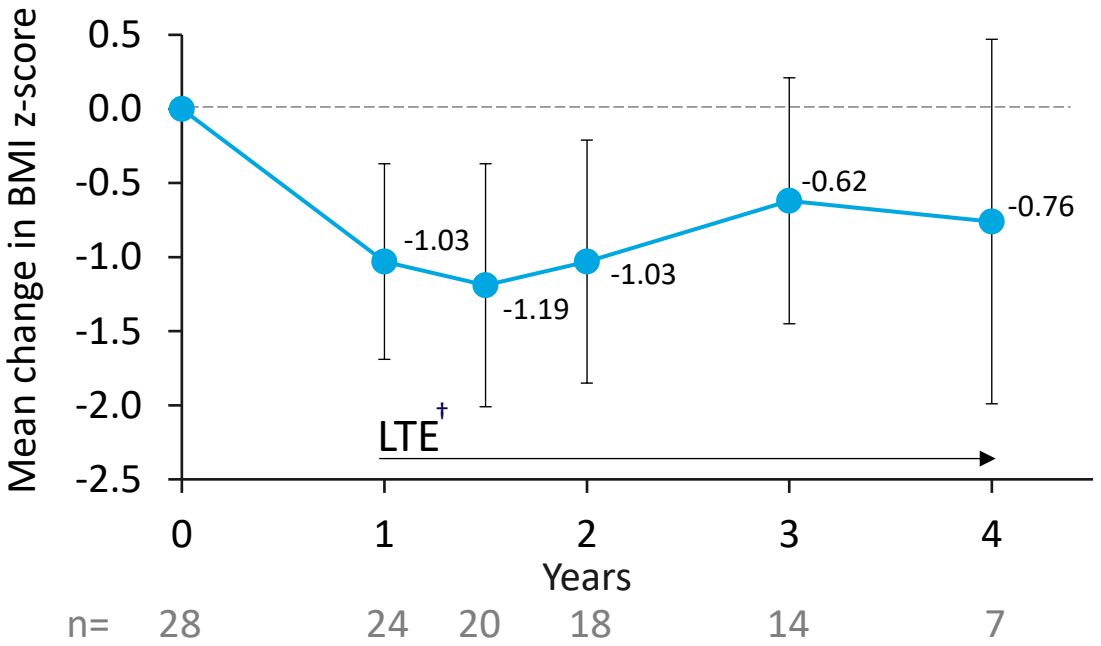


- In participants with POMC/LEPR deficiency, the mean percent change from baseline in BMI was −21.6% (SD, 19.1) at Year 5 (n=6)

A common reason for study discontinuation was that participants transitioned to commercial therapy after regulatory approval of setmelanotide. Data shown are for participants who were paediatric at index trial baseline, a portion of whom entered adulthood during the LTE; all available BMI data from these participants are shown. Error bars are the SD. *Not all participants received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin; SD, standard deviation.

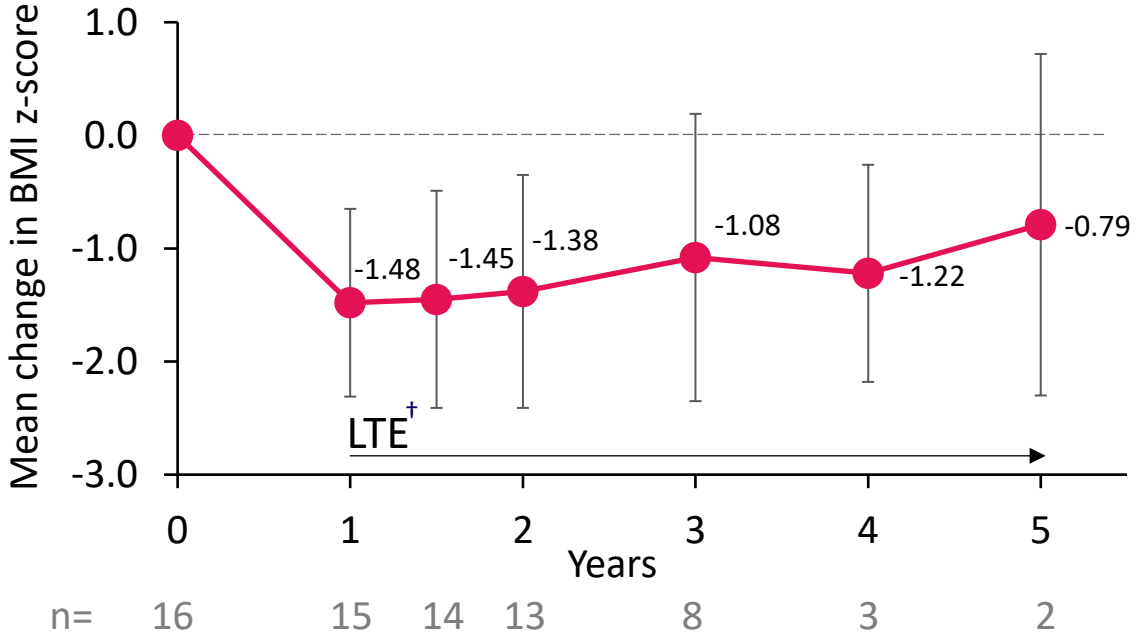
Setmelanotide treatment led to sustained reduction in BMI z-score* for paediatric participants with BBS or with POMC/LEPR deficiency

BBS



- In participants with BBS, the mean change from baseline in BMI z-score was –0.76 (SD, 1.23) at Year 4 (n=7)
  - 57.1% (4/7) achieved a ≥0.2 BMI z-score reduction from baseline at Year 4

POMC/LEPR



- In participants with POMC/LEPR deficiency, the mean change from baseline in BMI z-score was –0.79 (SD, 1.51) at Year 5 (n=2)
  - One of two participants achieved a ≥0.2 BMI z-score reduction from baseline at Year 5

A common reason for study discontinuation was that participants transitioned to commercial therapy after regulatory approval of setmelanotide. For participants who reached 18 years of age during the LTE, available z-score data from paediatric ages are shown here. Error bars are the SD. *BMI z-score calculated according to the World Health Organization 2007 method. †Not all participants received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin; SD, standard deviation.

Safety

n (%)	BBS N=28	POMC/LEPR N=16
Any AEs	28 (100)	15 (93.8)
Treatment-related AEs	28 (100)	15 (93.8)
Serious AEs	3 (10.7)	7 (43.8)
Serious treatment-related AEs	0	0
AE leading to study drug withdrawal	2 (7.1)	2 (12.5)
AE leading to death	0	0
AEs in ≥30% of either cohort		
Skin hyperpigmentation	21 (75.0)	15 (93.8)
Injection site pruritus	18 (64.3)	8 (50.0)
Injection site erythema	17 (60.7)	12 (75.0)
Injection site induration	14 (50.0)	5 (31.3)
Vomiting	13 (46.4)	6 (37.5)
Injection site bruising	12 (42.9)	4 (25.0)
Injection site pain	12 (42.9)	2 (12.5)
Injection site oedema	9 (32.1)	9 (56.3)
Nausea	8 (28.6)	10 (62.5)
Headache	8 (28.6)	8 (50.0)
Diarrhoea	7 (25.0)	6 (37.5)
Abdominal pain	3 (10.7)	5 (31.3)
Upper respiratory tract infection	3 (10.7)	7 (43.8)
Back pain	1 (3.6)	5 (31.3)

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

Conclusions

Sustained reductions in BMI and BMI z-score with setmelanotide support that early treatment with a targeted therapy should be considered in paediatric patients with BBS and POMC/LEPR deficiency, where hyperphagia and early-onset obesity are common clinical features

The safety profile of setmelanotide in paediatric participants with BBS and POMC/LEPR deficiency was generally consistent with that observed in previous clinical trials of setmelanotide, and no new safety concerns were identified during the follow-up period

Overall, the findings from this study support the clinical benefit of long-term setmelanotide treatment in paediatric populations with BBS or POMC/LEPR deficiency

BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin.

THANK YOU

We would like to thank the participants and caregivers, without whom this trial could not have been completed

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