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Introduction

- Bardet-Biedl syndrome (BBS), a rare neuroendocrine disease, is associated with certain genetic variants in the hypothalamic melanocortin-4 receptor (MC4R) pathway¹⁻⁴
- In BBS, disrupted MC4R pathway signaling can lead to hyperphagia (pathological, insatiable hunger) and early-onset obesity that has historically been resistant to medical treatment⁴⁻⁶
- In a pivotal Phase 3 clinical trial, treatment with the MC4R agonist setmelanotide was associated with clinically meaningful improvements in weight and hunger-related outcomes in participants with BBS and obesity at 1 year, followed by continued weight improvements up to 3 years of treatment with no new safety concerns^{1,7,8}

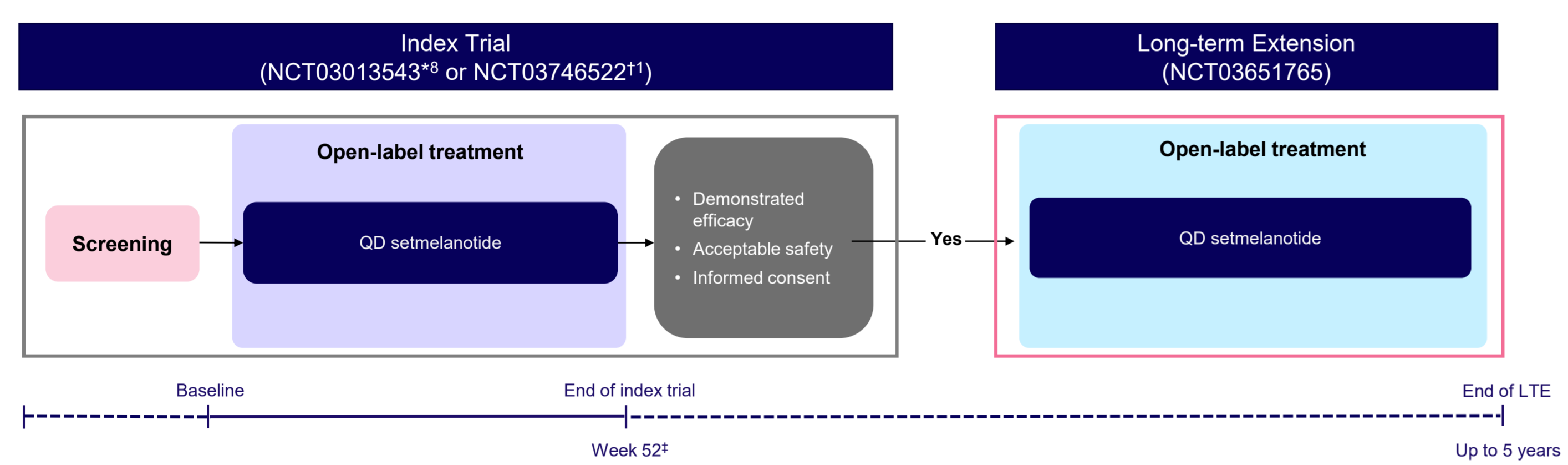
Objective

- To assess ongoing efficacy and safety over 5 years of setmelanotide treatment in participants with BBS in a long-term extension trial

Methods

- Participants who completed a Phase 2 (NCT03013543) or Phase 3 (NCT03746522) index trial and experienced clinically meaningful weight response with setmelanotide could continue treatment in a long-term extension trial (LTE; NCT03651765) (Figure 1)
- The current analysis assessed changes from baseline in body mass index (BMI) and BMI z-score (aged <18 years) in participants with BBS out to 5 years of setmelanotide treatment
- Data from all participants are presented out to Year 5; adult and pediatric subgroup results are presented out to Year 4 due to small sample sizes

Figure 1: Study design



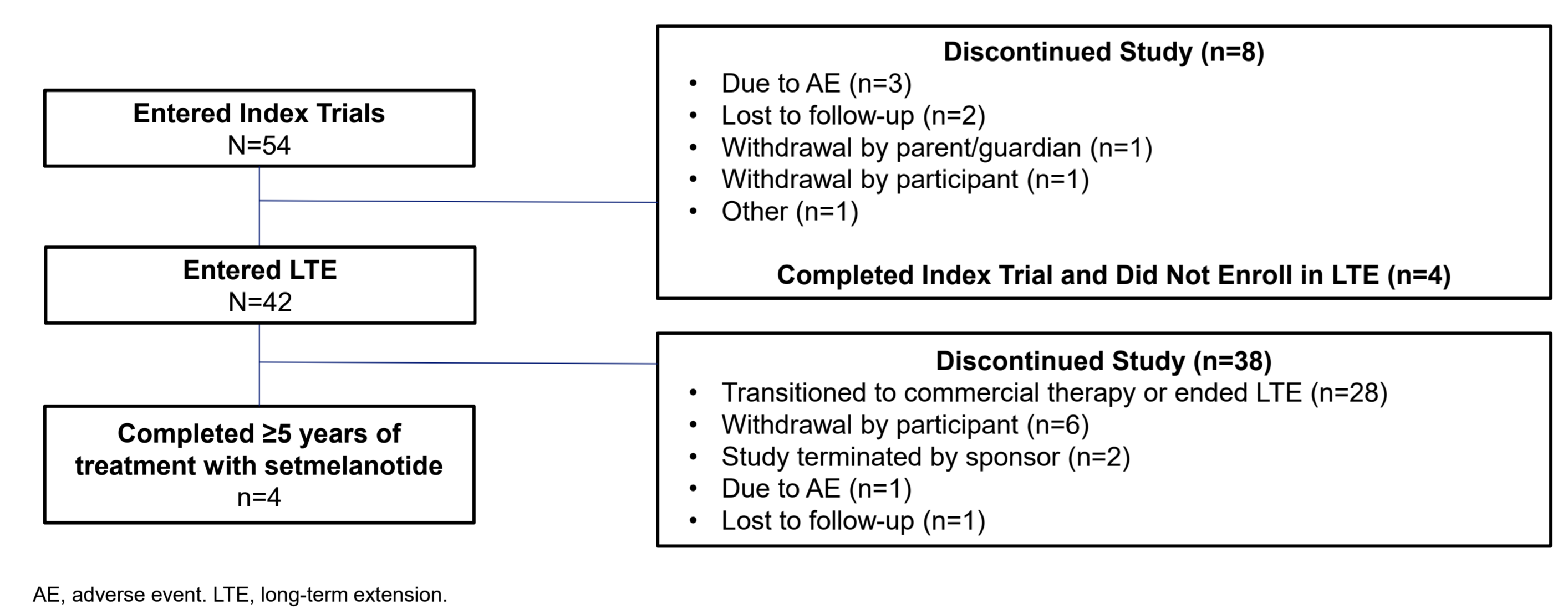
*Data from the Phase 2 index trial have been published in *Diabetes Obes Metab*.⁸ *Data from the Phase 3 index trial have been published in *Lancet Diabetes Endocrinol*.¹ †Not all participants received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. LTE, long-term extension; QD, once daily.

Results

Participant Disposition and Baseline Characteristics

- Fifty-four participants entered an index trial, of whom, 42 continued into the LTE (Figure 2)
- A common reason for study discontinuation was participants transitioned to commercial therapy after regulatory approval of setmelanotide

Figure 2: Participant disposition



- Baseline characteristics are listed in Table 1
- The mean (SD) BMI at baseline in all participants was 42.2 (9.2; n=53) kg/m²
- The mean (SD) BMI at baseline in participants ≥18 years old was 47.2 (6.7; n=25) kg/m²
- The mean (SD) BMI z-score at baseline in participants <18 years old was 4.26 (1.65; n=28)

Table 1: Characteristics at index trial baseline

	Setmelanotide N=54
Age, mean (SD; range), years	20.4 (11.8; 6-61)
Age, n (%)	
≥18	26 (48.1)
<18	28 (51.9)
Sex, n (%)	
Male	24 (44.4)
Female	30 (55.6)
Race, n (%)	
White	43 (79.6)
Black or African American	3 (5.6)
Asian	1 (1.9)
Other	7 (13.0)
Weight, mean (SD), kg	112.6 (33.3)
BMI, mean (SD), kg/m ²	42.2 (9.2)
BMI z-score (in participants <18 years old), mean (SD)*	4.26 (1.65)
Waist circumference, mean (SD), cm	119.0 (21.2)

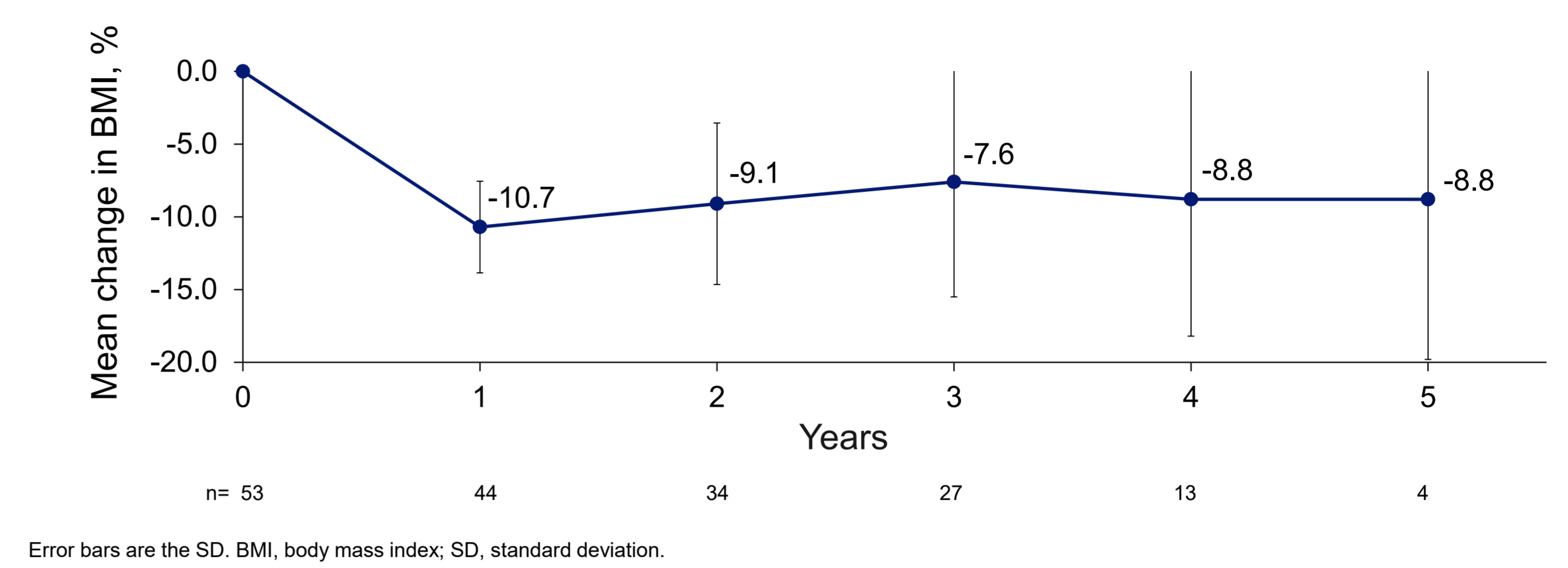
BMI, body mass index; SD, standard deviation.
*BMI z-score calculated according to the World Health Organization 2007 method.

Results (continued)

Efficacy

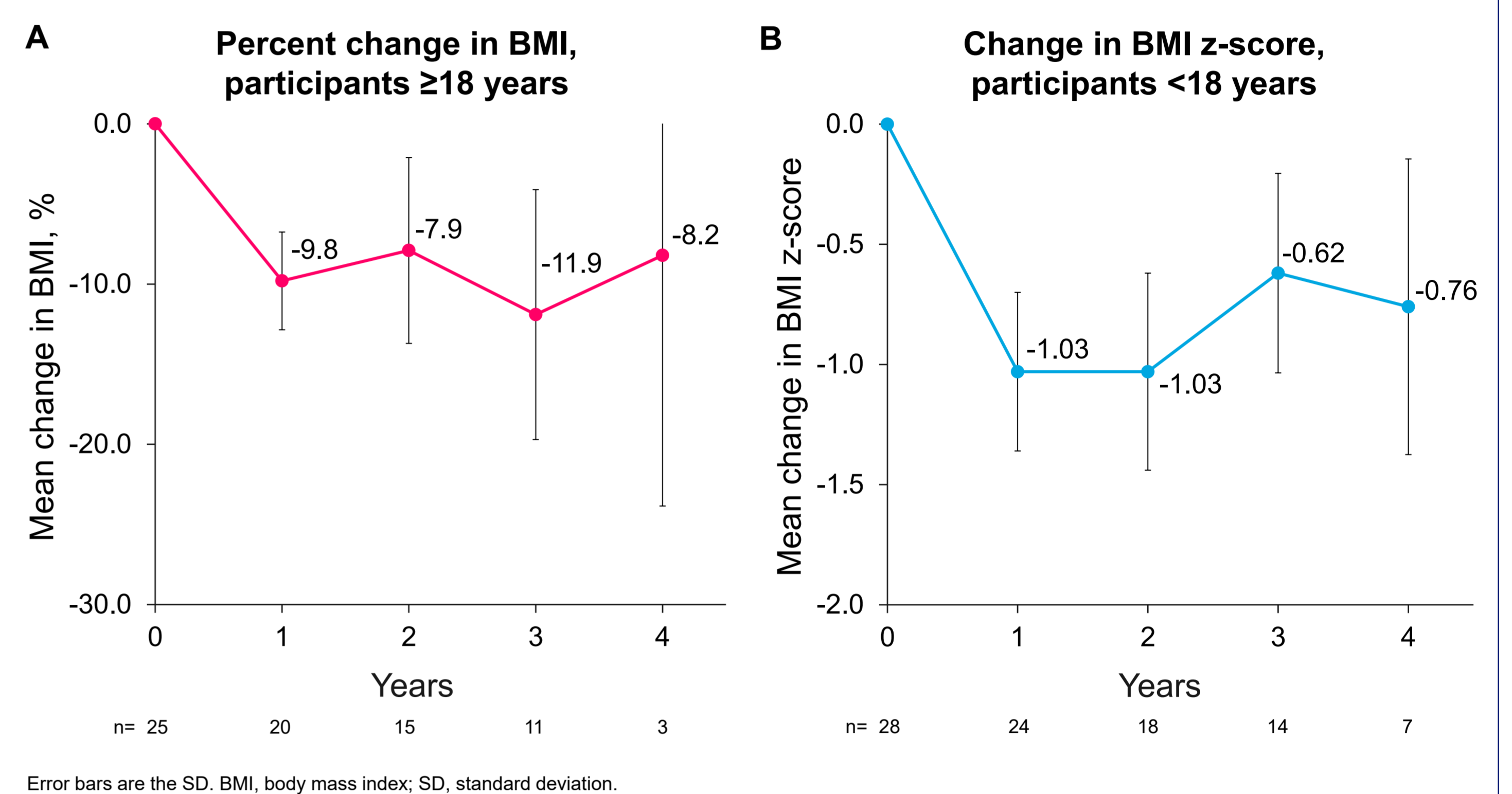
- At Year 5, the mean (SD) percent change from baseline in BMI was -8.8% (22.0%) in 4 participants (Figure 3)

Figure 3: Mean percent change from baseline in BMI for all participants



- The mean (SD) percent change from baseline in BMI in adults (≥18 years old) was -8.2% (31.3%) in 3 participants at Year 4 (Figure 4A)
- The mean (SD) change from baseline in BMI z-score in participants <18 years old was -0.76 (1.23) in 7 participants at Year 4 (Figure 4B)

Figure 4: Mean change from baseline in weight parameters by age category



Safety

- Skin hyperpigmentation (66.7%) and injection site erythema (53.7%) were the most commonly reported adverse events up to Year 5 (Table 2)

Table 2: Safety

n (%)	Setmelanotide N=54
Any AEs	54 (100)
Treatment-related AEs	54 (100)
Serious AEs	8 (14.8)
Treatment-related serious AEs	1 (1.9)
AE leading to study drug withdrawal	4 (7.4)
AE leading to death	0
AEs in ≥20% of participants	
Skin hyperpigmentation	36 (66.7)
Injection site erythema	29 (53.7)
Injection site pruritus	27 (50.0)
Injection site induration	22 (40.7)
Injection site bruising	20 (37.0)
Nausea	19 (35.2)
Vomiting	17 (31.5)
Headache	16 (29.6)
Injection site pain	16 (29.6)
COVID-19	13 (24.1)
Diarrhea	13 (24.1)
Injection site edema	13 (24.1)

AE, adverse event; COVID-19, coronavirus disease 2019.



Conclusions

- Continued treatment with setmelanotide for up to 5 years provided clinically relevant reductions in weight-related parameters in participants with BBS and obesity
- Additionally, these results further support the potential benefits of beginning early intervention with targeted treatment to address the early-onset obesity often observed in this patient population

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