# Weight outcomes at 6 years of setmelanotide in patients with POMC or LEPR deficiency and obesity

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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]
- Patients with proopiomelanocortin (POMC) deficiency (including variants in *POMC* or proprotein convertase subtilisin/kexin type 1 [*PCSK1*]) or leptin receptor (LEPR) deficiency due to biallelic gene variants have disrupted MC4R signaling[3-7]
  - Altered MC4R signaling can lead to hyperphagia (pathological, insatiable hunger) and early-onset and severe obesity that has historically been resistant to medical treatment[3-7]
- In pivotal Phase 3 clinical trials, treatment with the MC4R agonist setmelanotide was associated with clinically meaningful improvements in weight and hunger-related outcomes in participants with POMC or LEPR deficiency at 1 year, followed by continuous weight improvements up to 4 years with no new safety concerns[8]

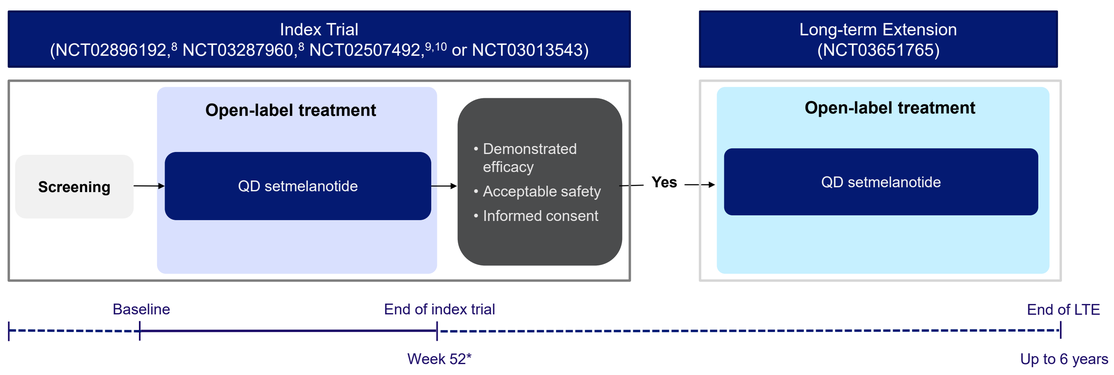
## Objective

- To assess the efficacy and safety of up to 6 years of setmelanotide treatment in participants with POMC or LEPR deficiency and obesity

## Methods

- Participants with POMC or LEPR deficiency who completed a prior clinical trial with setmelanotide and experienced clinically meaningful weight response could continue treatment in a long-term extension trial (LTE; NCT03651765) (Figure 1)
  - Key exclusion criteria for the index trials were recent diet, exercise, or gastric bypass surgery resulting in weight loss or stabilization, significant or concerning dermatologic findings (eg, melanoma or skin lesions), or a history of suicidal ideation or behavior, or moderate-to-severe renal dysfunction
- The current analysis assessed changes from index trial baseline in body mass index (BMI) and BMI z-score (aged <18 years) at up to 6 years follow-up

**Figure 1.** Study design



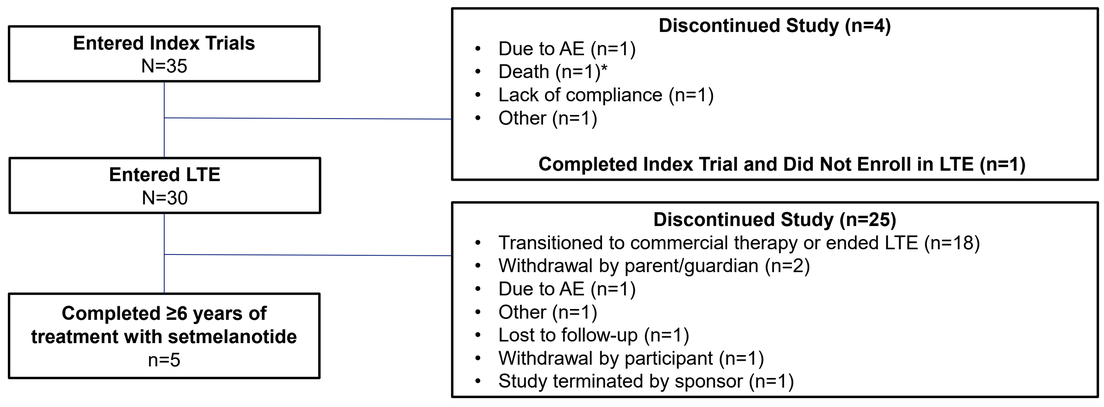

BMI, body mass index; LTE, long-term extension; QD, once daily.
*Not all participants received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time.

## Results

### Participant Disposition and Baseline Characteristics

- Thirty-five participants entered an index trial, of whom, 30 entered the LTE (Figure 2)
  - A common reason for trial discontinuation was participants transitioned to commercial therapy after regulatory approval of setmelanotide

**Figure 2.** Participant disposition




*One participant died in a traffic accident, deemed not related to treatment. AE, adverse event; LTE, long-term extension.

- The mean (SD) BMI at baseline in all participants was 44.1 (11.3; n=35) kg/m$^2$ (Table 1)
- The mean (SD) BMI z-score at baseline in participants <18 years old was 3.86 (0.75; n=16)

**Table 1.** Characteristics at index trial baseline

| | Setmelanotide N=35 |
|---|---|
| **Age, mean (SD; range), years** | 19.5 (7.6; 7-37) |
| **Age, n (%)** | |
| ≥18 | 19 (54.3) |
| <18 | 16 (45.7) |
| **Sex, n (%)** | |
| Male | 18 (51.4) |
| Female | 17 (48.6) |
| **Race, n (%)** | |
| White | 24 (68.6) |
| Black or African American | 1 (2.9) |
| Other | 10 (28.6) |
| **Weight, mean (SD), kg** | 123.8 (36.4) |
| **BMI, mean (SD), kg/m$^2$** | 44.1 (11.3) |
| **BMI z-score (in participants <18 years old), mean (SD)*** | 3.86 (0.75) |
| **Waist circumference, mean (SD), cm** | 122.7 (20.8) |

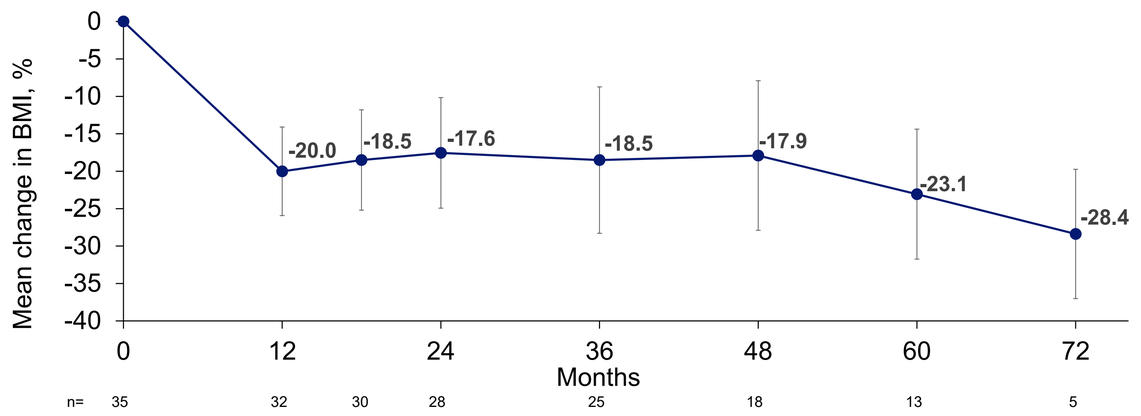
BMI, body mass index; SD, standard deviation.
*BMI z-score calculated according to the World Health Organization 2007 method.

## Results (continued)

### Efficacy

- At Year 6, the mean (SD) percent change in BMI from baseline in 5 participants was –28.4% (17.3%; Figure 3)

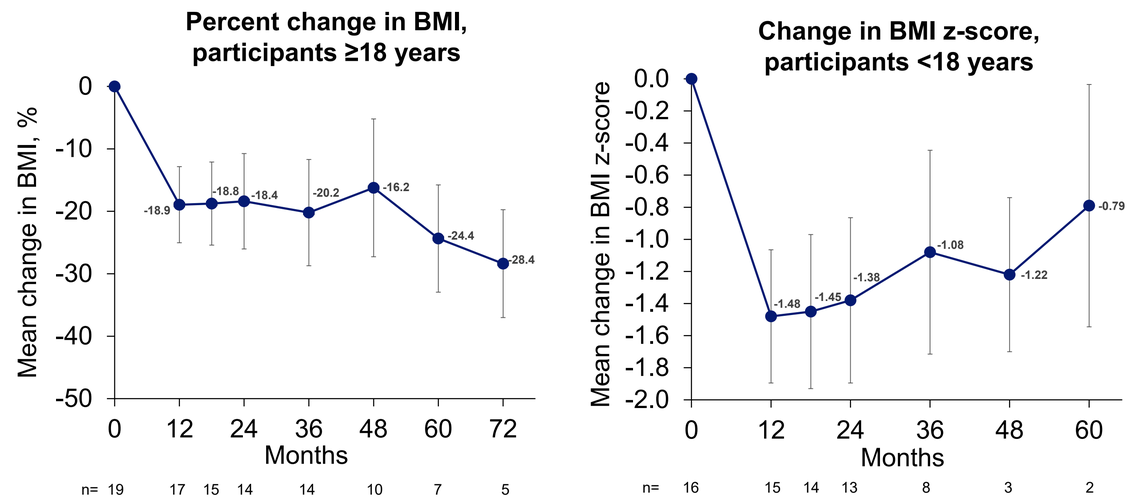
**Figure 3.** Mean percent change from baseline in BMI for all participants




Error bars are the SD; BMI, body mass index; SD, standard deviation.

- In participants aged ≥18 years, the mean (SD) percent change in BMI from baseline was –28.4% (17.3%) in 5 participants at Year 6 (n=5; Figure 4)
- The mean (SD) change in BMI z-score from baseline for participants aged <18 years old was –0.79 (1.51) at Year 5 (n=2; Figure 4)
  - There were no pediatric participants who reached 6 years of treatment

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




Error bars are the SD; BMI, body mass index; SD, standard deviation.

### Safety

- Skin hyperpigmentation (28/35; 80.0%) and injection site erythema (24/35; 68.6%) were the most commonly reported adverse events up to Year 6 (Table 2)

**Table 2.** Safety

| n (%) | Setmelanotide N=35 |
|---|---|
| **Any AEs** | 30 (85.7) |
| **Treatment-related AEs** | 30 (85.7) |
| **Serious AEs** | 11 (31.4) |
| **Treatment-related serious AEs** | 0 |
| **AE leading to study drug withdrawal** | 4 (11.4) |
| **AE leading to death** | 1 (2.9)* |
| **AEs in ≥30% of participants** | |
| Skin hyperpigmentation | 28 (80.0) |
| Injection site erythema | 24 (68.6) |
| Headache | 18 (51.4) |
| Injection site pruritus | 18 (51.4) |
| Nausea | 18 (51.4) |
| Injection site edema | 16 (45.7) |
| Diarrhea | 14 (40.0) |
| Back pain | 11 (31.4) |
| COVID-19 | 11 (31.4) |
| Vomiting | 11 (31.4) |

*One participant died in a traffic accident, deemed not related to treatment.
AE, adverse event; COVID-19, coronavirus disease 2019.

## Conclusions

- These data further demonstrate the long-term weight improvements with setmelanotide treatment in participants with POMC or LEPR deficiency and obesity
- Furthermore, the mean BMI z-score reduction in participants <18 years of age over the course of 5 years of treatment with setmelanotide further reinforces the potential benefits of beginning early intervention with a targeted therapy in this patient population, where early-onset and severe obesity is a common clinical feature

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**References: 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.** Farooqi et al. *Diabetes*. 2006;55(9):2549-25537. **5.** Folon et al. *Lancet Diabetes Endocrinol*. 2023;11(3):182-190. **6.** Montague et al. *Nature*. 1997;387:903-908. **7.** Clément et al. *Nature*. 1998;26;392(6674):398-401. **8.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **9.** Kühnen et al. *N Engl J Med*. 2016;375:240-246. **10.** Clément et al. *Nat Med*. 2018;24:551-555.

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