Body Mass Index and Weight Reductions in Patients With Obesity Due to Heterozygous Variants in *POMC*, *PCSK1*, or *LEPR* After 1 Year of Setmelanotide

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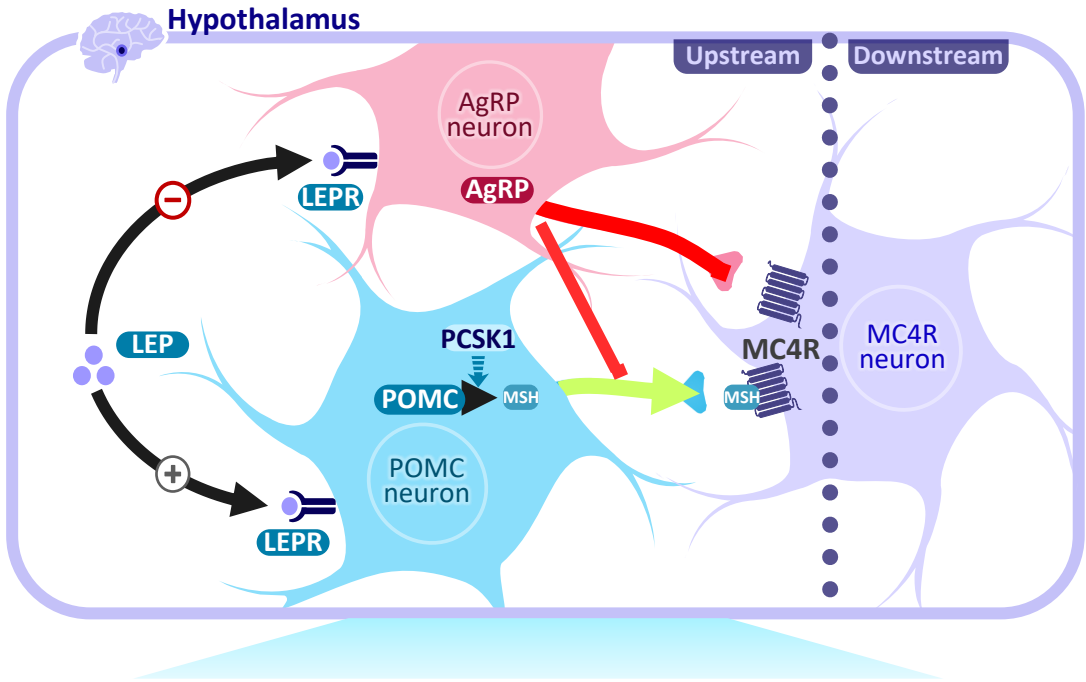
The MC4R Pathway Regulates Energy Balance[1]

Heterozygous variants in key genes upstream of MC4R (*POMC*, *LEPR*, *PCSK1*) may impair signaling in the MC4R pathway[2] leading to early-onset, severe obesity[3]

The MC4R agonist setmelanotide can reduce weight and hunger after 3 months in patients with heterozygous variants in these genes[4]

This long-term extension study investigates continued efficacy in an additional year of setmelanotide treatment in patients with heterozygous variants in *POMC*, *LEPR*, or *PCSK1*

Normal signaling in the MC4R pathway[1]

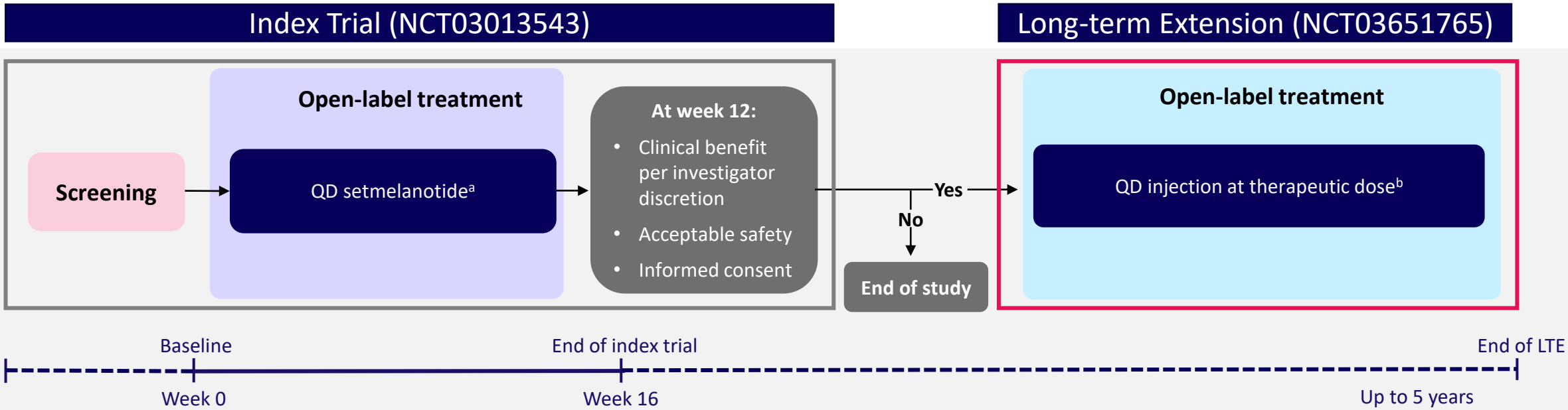


Decrease food intake | **Decrease body weight** | **Increase energy expenditure**

AgRP, agouti-related peptide; LEP, letpin; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Yazdi et al**.** *PeerJ***.** 2015;3:e856. **2.** Huvenne et al. *Obes Facts.* 2016;9:158-173. **3.** Nordang et al. *Mol Genet Metab.* 2017;121(1):51-56. **4.** Farooqi et al. Presented at: Overcoming Obesity; September 23-26, 2021; Chicago, IL.

Phase 2 Trial (NCT03651765) for Long-Term Extension of Setmelanotide for Patients Who Have Completed a Trial of Setmelanotide



Key LTE inclusion criteria

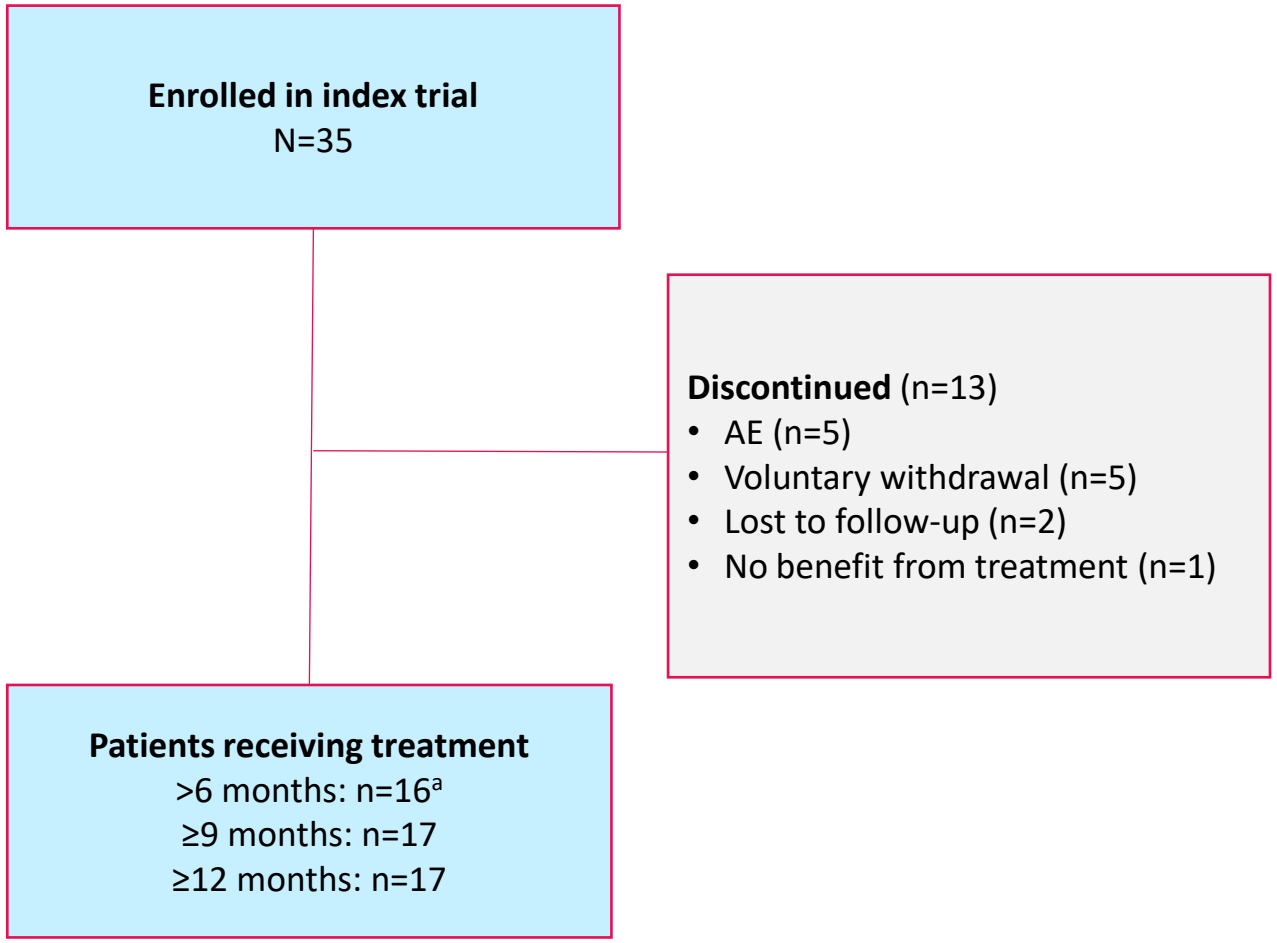
- Rare genetic disease of obesity
- ≥6 years of age
- Demonstrated clinical benefit and safety in index trial[c]
  - As determined by primary investigator

Key LTE exclusion criteria

- Dermatologic lesions related to melanoma
- History of severe liver disease or injury
- Glomerular filtration rate <30 mL/min

[a]Setmelanotide initiated at 1.0 mg QD for those ≥18 years old and 0.5 mg QD for those ≥12 to <18 years old. Doses were titrated upward for 2 to 12 weeks to determine the individual therapeutic dose for each patient (maximum 3.0 mg QD). [b]Long-term extension will continue at the same dose at completion of index trial. [c]Index trial data previously presented at Overcoming Obesity; October 14-16, 2021; Virtual.
LTE, long-term extension; QD, once daily.

Disposition and Baseline Demographics



Index trial baseline characteristics	Total (N=35)
Age, years	
Mean (SD)	**39.46 (14.64)**
Range	**15-68**
Sex, n (%)	
Female	**11 (31.4)**
Male	**24 (68.6)**
Race, n (%)	
White	**31 (88.6)**
Black or African American	**4 (11.4)**
Ethnicity, n (%)	
Hispanic or Latino	**1 (2.9)**
Not Hispanic or Latino	**34 (97.1)**

Data cutoff: October 29, 2021.
[a]One patient missed the 6-month visit.
AE, adverse event; SD, standard deviation.

Setmelanotide Treatment Was Associated With BMI Reduction in Patients With Heterozygous Variants in *POMC*, *PCSK1*, or *LEPR*

–8.7% mean change in BMI after 12 months of treatment

	Index baseline (N=35)	**% change at Month 6** (n=16)	**% change at Month 9** (n=17)	**% change at Month 12** (n=17)
BMI, mean (SD)	**50.4 kg/m^2** (9.3)	**–7.9** (7.2)	**–9.0** (8.6)	**–8.7** (8.2)

Data cutoff: October 29, 2021.
BMI, body mass index; SD, standard deviation.

Setmelanotide Treatment Was Associated With Reduction in Body Weight in Patients ≥18 Years Old After 12 Months of Treatment

After 12 months:

–10.2% mean change in body weight in patients ≥18 years old[a]

53.3% achieved ≥10% loss in body weight

	Index baseline (N=35)	% change at Month 6 (n=15)	% change at Month 9 (n=14)	% change at Month 12 (n=15)
Body weight, mean (SD)	**143.0 kg/m^2** (28.7)	**–8.9** (6.82)	**–11.7** (7.3)	**–10.2** (7.9)

Data cutoff: October 29, 2021.

[a]Weight-related parameters were analyzed by adult and pediatric subgroups separately to minimize dilution of treatment effect and evaluate on the basis of appropriate measures per age group.

SD, standard deviation.

Setmelanotide Treatment Was Generally Well Tolerated in Patients With Heterozygous Variants in *POMC*, *PCSK1*, or *LEPR*

Treatment-emergent AEs	n (%)
Treatment related	34 (97.1)
Serious	3 (8.6)
Serious treatment related	0 (0)
Leading to drug discontinuation	5 (14.3)
Leading to death	0 (0)

Treatment-emergent AEs occurring in ≥20% of patients[a]	n (%)
Skin hyperpigmentation	20 (57.1)
Fatigue	14 (40)
Injection site pruritus	14 (40)
Injection site erythema	13 (37.1)
Injection site pain	7 (20)
Melanocytic nevus	7 (20)
Nausea	18 (51.4)

[a]Treatment-emergent serious AEs were experienced by 3 patients (8.6%; n=35), including acute myocardial infarction (2.9%; n=1), gastrointestinal hemorrhage (2.9%; n=1), melaena (2.9%; n=1), endometrial cancer (2.9%; n=1), and pulmonary embolism (2.9%; n=1). None of these events were considered related to treatment. AE, adverse event.

Summary and Conclusions

- In patients with obesity due to heterozygous variants in *POMC*, *PCSK1*, or *LEPR*, setmelanotide treatment was associated with reduced BMI and weight loss
- Setmelanotide demonstrated continued efficacy for up to 12 months of treatment
- Setmelanotide was generally well tolerated, with no new safety concerns
- These findings support continued investigation into setmelanotide treatment, currently underway in the Phase 3 EMANATE trial (NCT05093634)

BMI, body mass index.