Efficacy and Safety of the MC4R Agonist Setmelanotide in POMC Deficiency Obesity: A Phase 3 Trial

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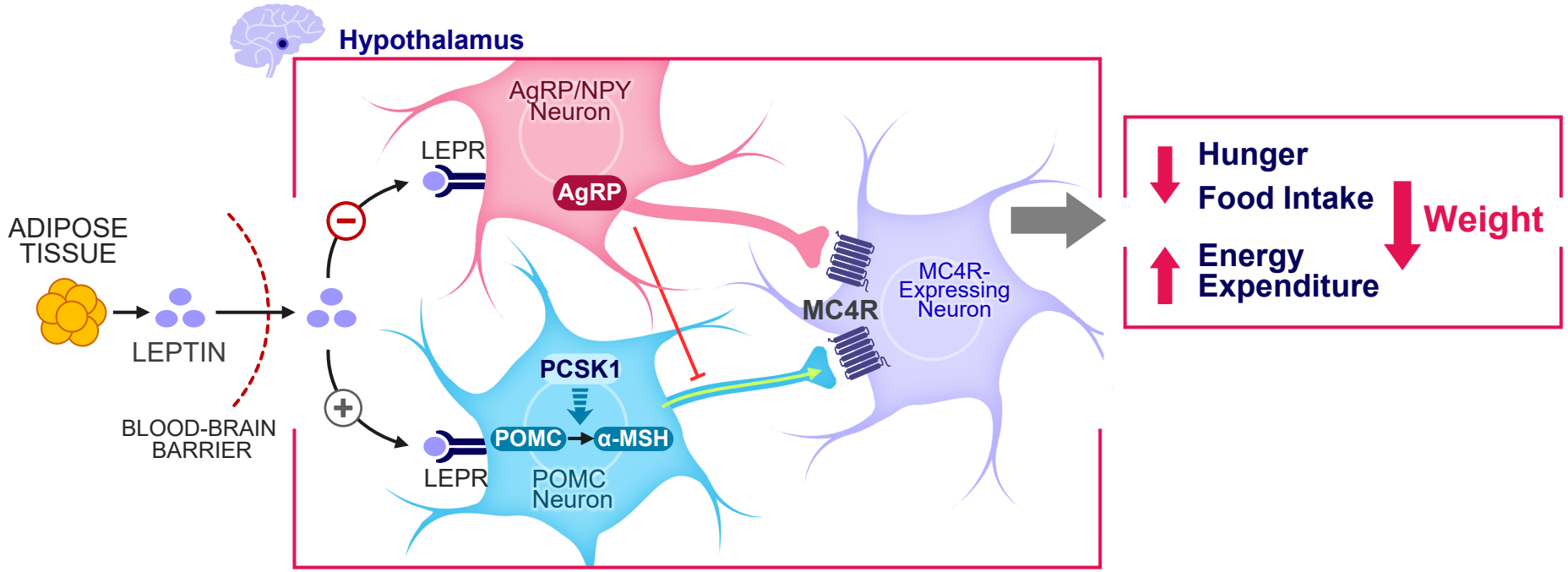
Rhythm Pharmaceuticals

Melanocortin Signaling Is Crucial for Regulation of Body Weight[1,2]

- Body weight is regulated by the hypothalamic central melanocortin pathway
- In response to leptin signaling, POMC is produced in POMC neurons and is cleaved by protein convertase subtilisin/kexin type 1 into α-MSH and β-MSH
- α-MSH and β-MSH bind to the MC4R, which decreases food intake and increases energy expenditure, thereby promoting a reduction in body weight

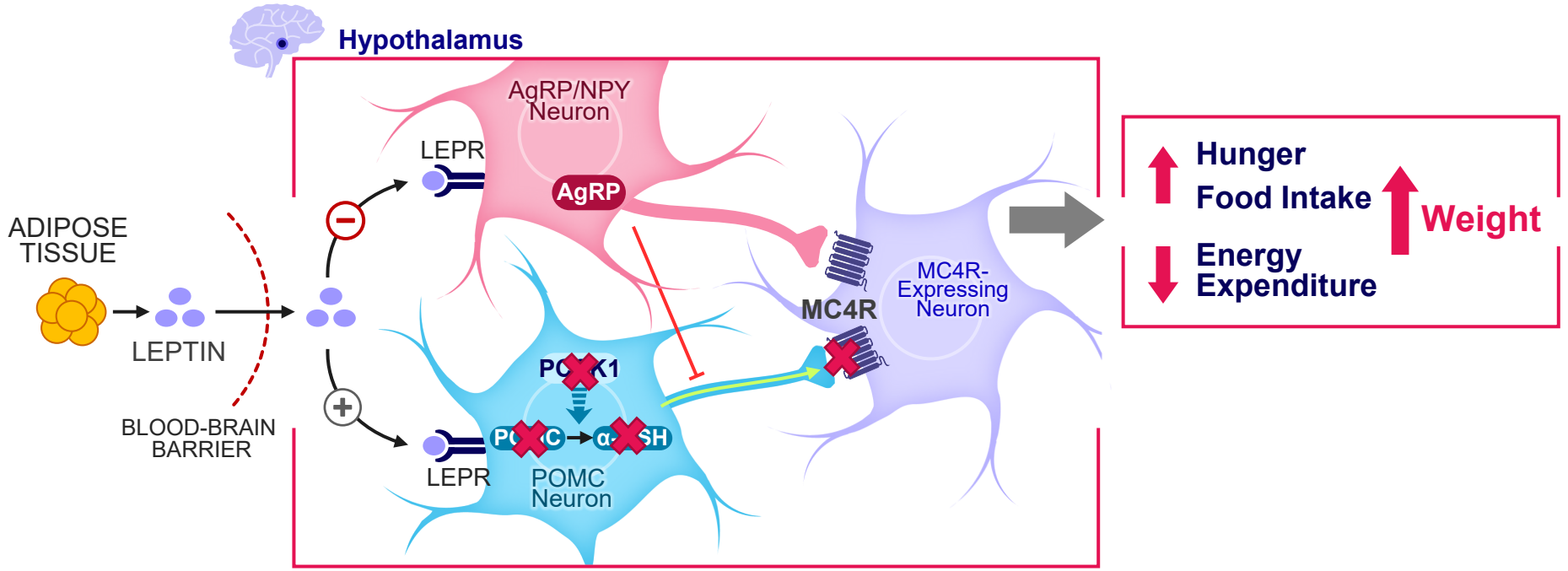


AgRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Yazdi et al. *PeerJ*. 2015;3:e856. **2.** Shen et al. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863:2477-2485.

Rare Genetic Variants in *POMC* and *PCSK1* Are Associated With Early-Onset Severe Obesity and Hyperphagia

- Obesity is a disease caused by environmental and genetic factors, including common or rare genetic variants that can impair gene expression or function[1,2]
- Rare genetic variants in the central melanocortin MC4R pathway, including variants in *POMC* and *PCSK1*, are characterized by early-onset severe obesity and hyperphagia[3]



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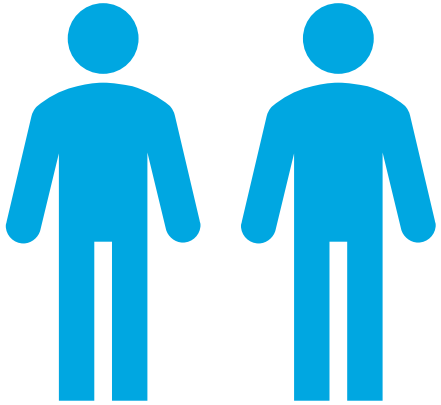
1. van der Klaauw and Farooqi. *Cell*. 2015;161:119-132. **2.** Speliotes et al. *Nat Genet*. 2010;42:937-948. **3.** Huvenne et al. *Obes Facts*. 2016;9:158-173.

Setmelanotide Is an MC4R Agonist That Targets the Impaired Central Melanocortin Pathway

Results from a phase 2 study showed that setmelanotide, an MC4R agonist, reduced weight in 2 patients with POMC deficiency obesity[1]

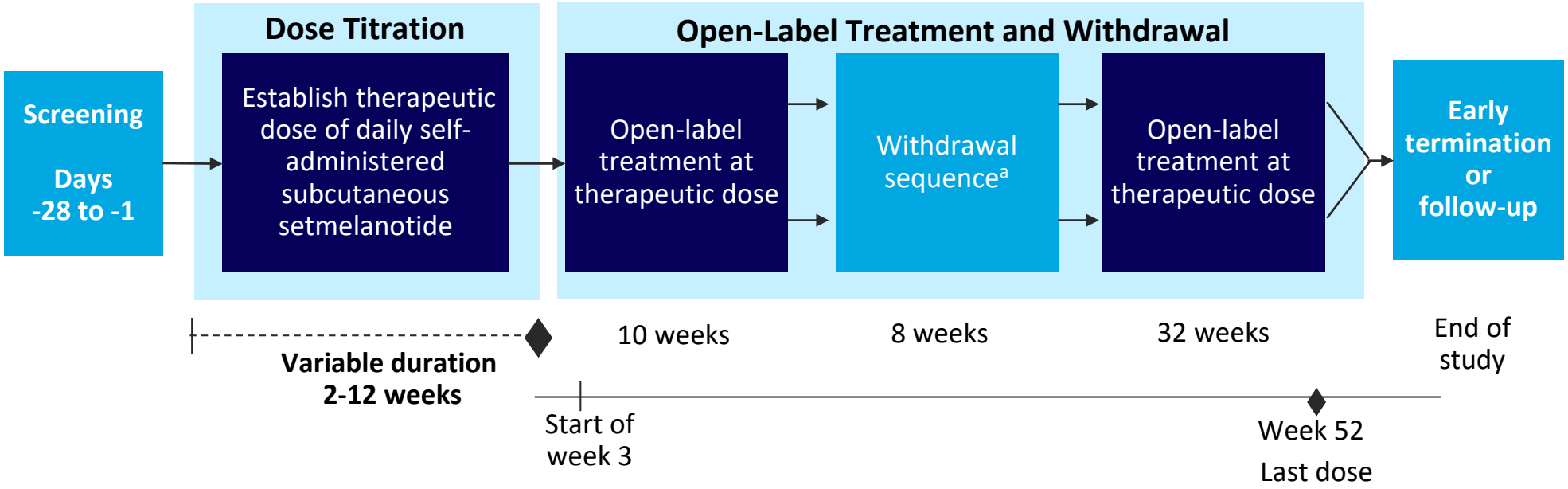


This multicenter, placebo-controlled, phase 3 trial investigated the efficacy and safety of setmelanotide in individuals with POMC or PCSK1 deficiency obesity

MC4R, melanocortin 4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Kühnen et al. *N Engl J Med*. 2016;375:240-246.

Phase 3 Study Design



Participants who lost ≥5 kg weight (or ≥5% if <100 kg) in the first open-label active treatment phase entered an 8-week, placebo-controlled phase, inclusive of a 4-week placebo withdrawal period

[a]Of the 9 participants who entered the placebo withdrawal period, 8 received treatment during the first 4 weeks and then placebo during the subsequent 4 weeks; 1 received placebo during the first 4 weeks and then was initiated back on treatment for the second 4 weeks.

Endpoints and Inclusion Criteria

Primary endpoint:

- Proportion of participants who achieved ≥10% weight loss

Key secondary endpoints:

- Mean percent change in body weight
- Mean percent change in "most hunger" score[a]
- Proportion of participants who achieved ≥25% reduction in "most hunger" score

Post hoc analysis:

- BMI Z-scores for participants aged <19 years

Key inclusion criteria

- Biallelic for loss-of-function *POMC or PCSK1* variants (homozygote or compound heterozygote)
- Adults (aged ≥18 years) with BMI of ≥30 kg/m^2
- Children or adolescents (aged ≥6 years to <18 years) with weight of ≥97th percentile for age

BMI, body mass index.

[a]"Most hunger" score was determined on a 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"

Ten Participants With POMC or PCSK1 Deficiency Obesity Were Enrolled

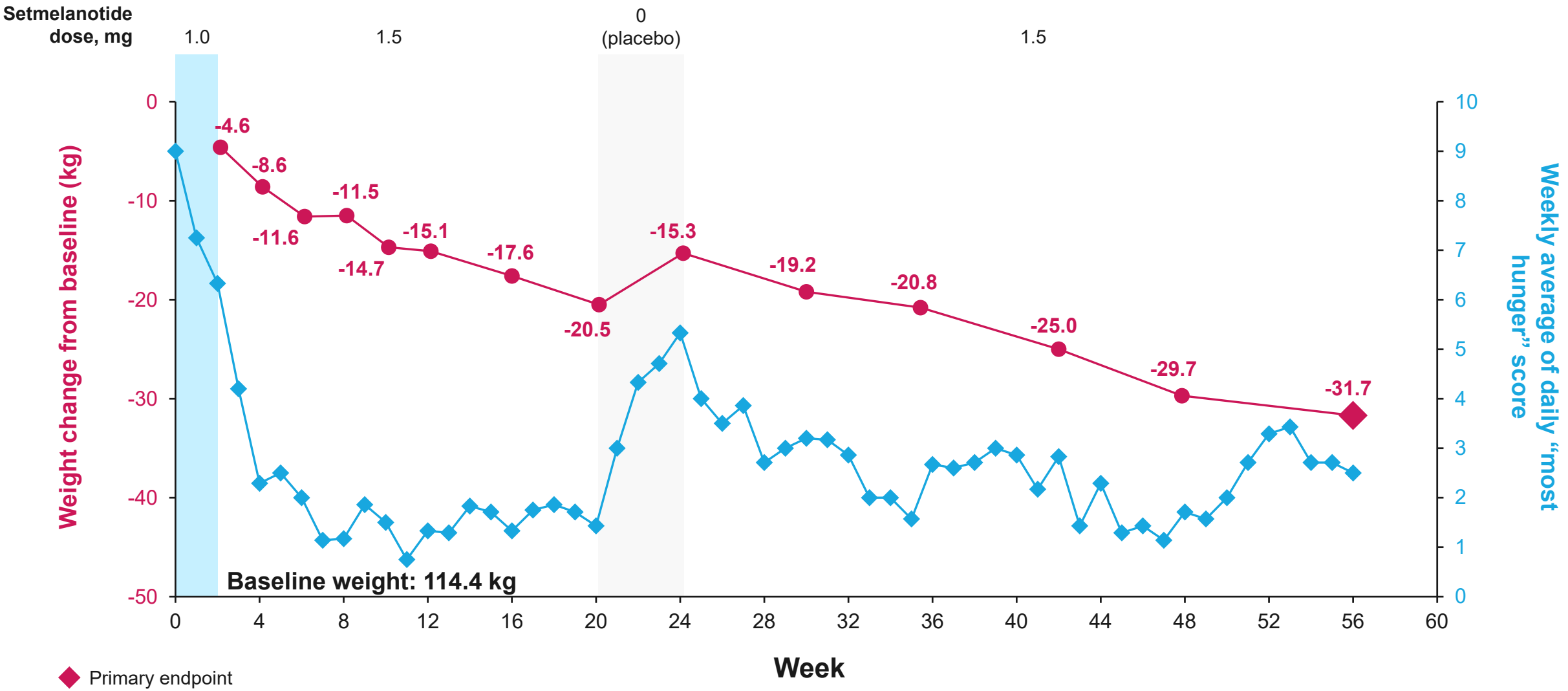
Baseline Characteristics	
Genotype, n (%)	
POMC	9 (90)
PCSK1	1 (10)
Age, mean (range), years	18.4 (11-30)
Male, n (%)	5 (50)
Ethnicity, n (%)	
Hispanic and Latino	1 (10)
Not Hispanic and Latino	8 (80)
Unknown	1 (10)
Weight, mean (range), kg	118.7 (55.9-186.7)
BMI, mean (range), kg/m^2	40.4 (26.6-53.3)
"Most hunger" score, mean (range)[a]	8.0 (7-9)

9 participants completed the trial; 1 participant discontinued[b]

BMI, body mass index; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

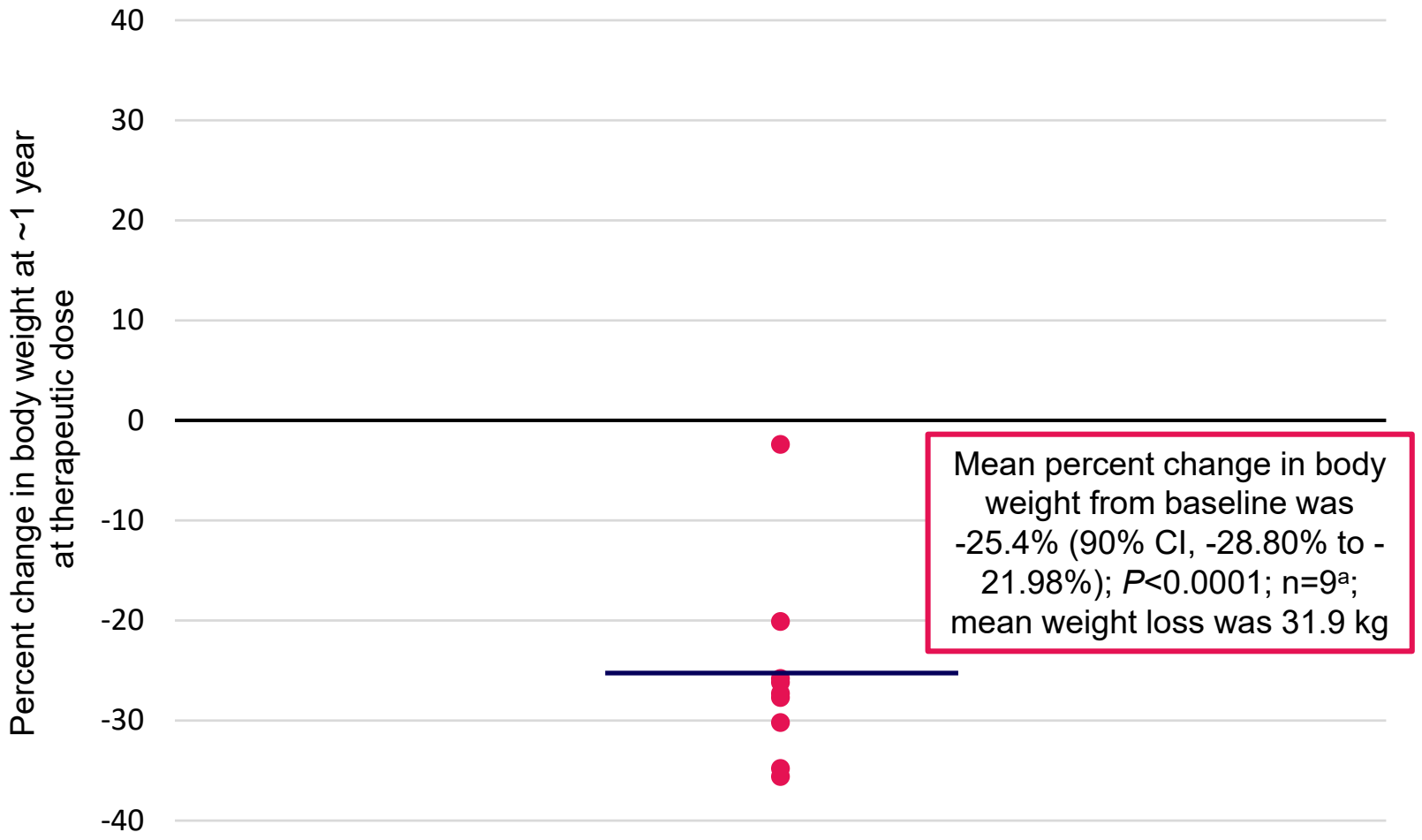
[a]"Most hunger" score was determined on a 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" [b]Participant with POMC deficiency obesity withdrew during the first open-label treatment phase because they did not meet the weight loss threshold.

Body Weight and Hunger Reduction in Patients With POMC Deficiency Obesity Treated With Setmelanotide for ~1 Year



Setmelanotide Was Associated With Significant Weight Reductions Over ~1 Year at Therapeutic Dose

8 of 10 participants (80% [90% CI, 49.31%–96.32%]; *P*<0.0001) achieved the primary endpoint threshold of ≥10% weight loss from baseline



The participant with PCSK1 deficiency obesity who did not meet the primary endpoint had confounding comorbidities and received treatment with risperidone for ~20 weeks, which made responses difficult to assess. The second participant who did not meet the primary endpoint was later determined to possibly not have had a loss-of-function variant in *POMC*.

[a]Endpoint analyzed in the evaluable population, which included participants who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase.

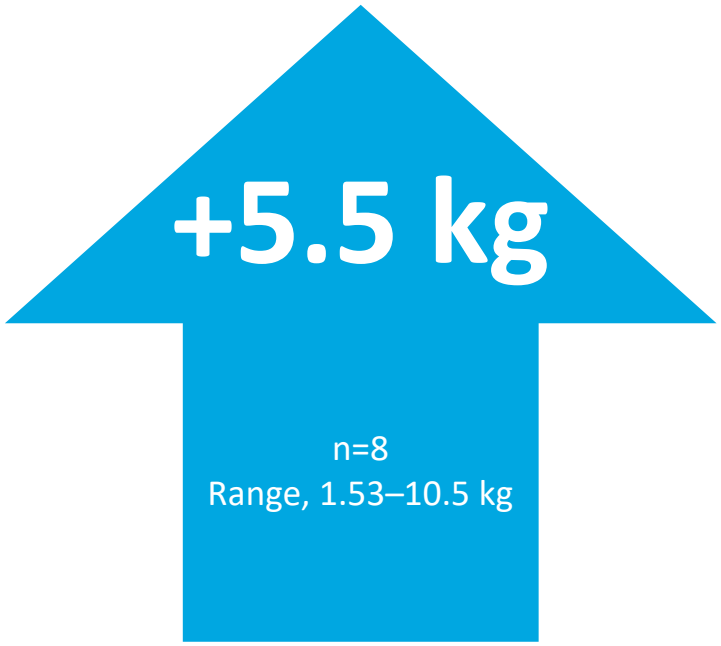
Setmelanotide Was Associated With Significant Reductions in "Most Hunger" Score Over ~1 Year at Therapeutic Dose

"Most Hunger" score parameter (n=7)[a]	Mean (SD)	Range
Baseline	8.1 (0.78)	7.0 to 9.0
~1 year at therapeutic dose	5.8 (2.02)	3.0 to 8.0
Percent change at ~1 year at therapeutic dose, % *P* value	-27.1 (28.11) *P*=0.0005	-72.0 to -1.0

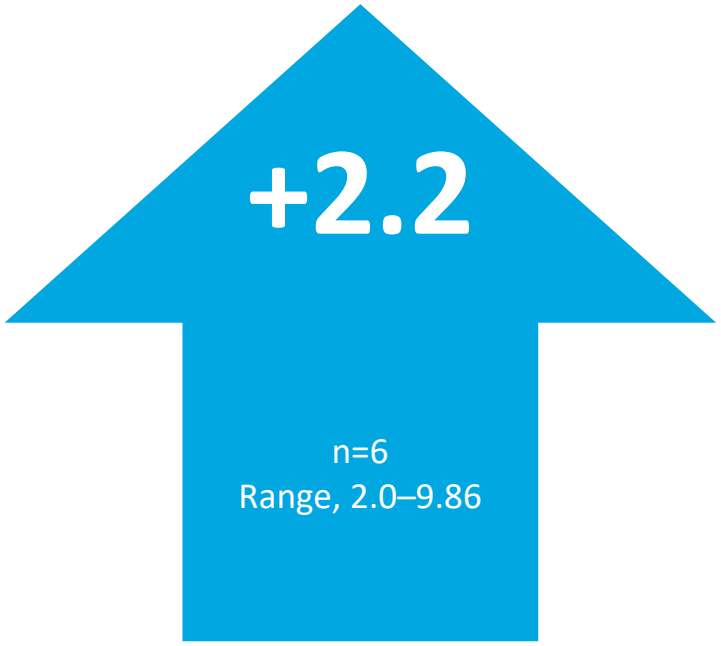
4 of 8 participants (50%) had ≥25% reduction in "most hunger" score from baseline (*P*=0.0004)[b]

[a]Endpoint analyzed in the evaluable population, which included participants who were aged ≥12 years and who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase. [b]Endpoint analyzed in the evaluable population, which included participants who were aged ≥12 years and who received at least 1 dose of setmelanotide.
"Most hunger" score is based on 0 to 10 Likert scale from the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"
SD, standard deviation.

Setmelanotide Withdrawal Was Associated With Increases in Weight and Hunger Score During the 4-Week Placebo Withdrawal Period



Mean weight change

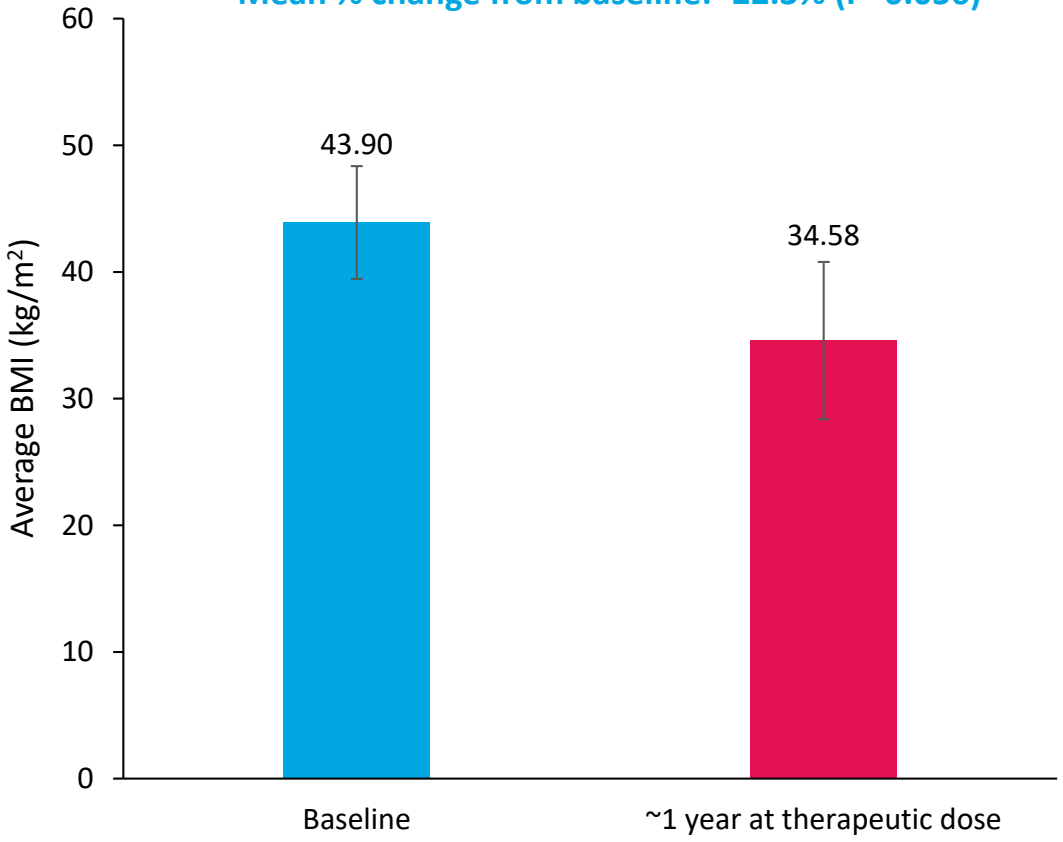


Change in mean "most hunger"

Setmelanotide Was Associated With Reductions in BMI and BMI Z-Score Over ~1 Year at Therapeutic Dose

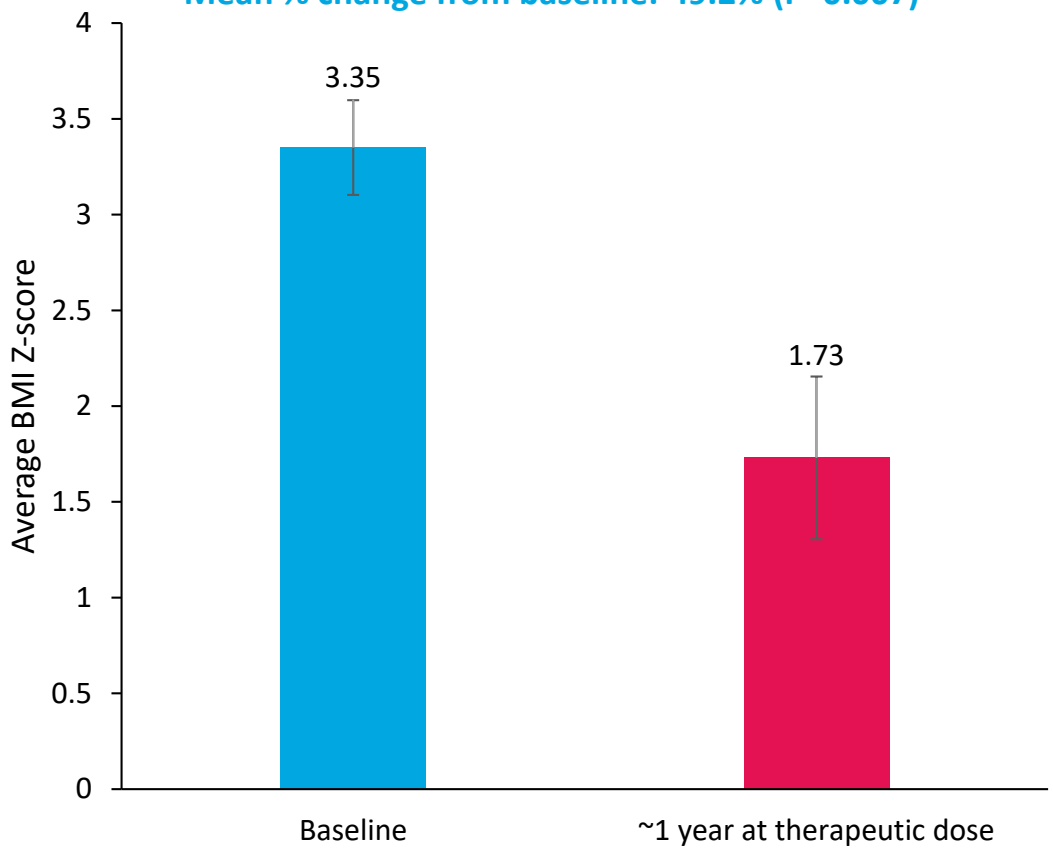
Participants aged ≥19 years (n=4)

Mean change from baseline: -9.3 kg/m²
Mean % change from baseline: -22.3% (P=0.056)



Participants aged <19 years (n=6)

Mean change from baseline: -1.6
Mean % change from baseline:-49.2% (P=0.007)



BMI, body mass index. Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of N.

Effect of Setmelanotide on BMI and BMI Z-Score

	Baseline	~1 year at therapeutic dose	Percent change from baseline
Participants aged ≥19 years, mean (SD) BMI, kg/m^2 (n=4)	43.90 (8.91)	34.58 (12.42)	-22.33 (14.75) *P*=0.056
Participants aged <19 years, mean (SD) BMI Z-score (n=6)	3.35 (0.61)	1.73 (1.04)	-49.18 (27.20) *P*=0.007

Setmelanotide was associated with reductions in BMI and significant reductions in BMI Z-scores

BMI, body mass index; SD, standard deviation.

Effect of Setmelanotide on Vital Signs

Parameter (N=10)	Baseline	~1 year at therapeutic dose	Percent change from baseline
Mean (SD) diastolic blood pressure, mm Hg	73.13 (10.75)	71.50 (9.17)	-1.81 (6.27) *P*=0.384
Mean (SD) systolic blood pressure, mm Hg	111.57 (7.78)	109.83 (6.12)	-1.355 (5.11) *P*=0.423
Mean (SD) heart rate, beats/min	81.03 (12.08)	75.37 (7.25)	-5.85 (11.44) *P*=0.140

Setmelanotide was not associated with changes in blood pressure or heart rate

SD, standard deviation.

Setmelanotide Was Well Tolerated in Individuals With POMC or PCSK1 Deficiency Obesity

Parameter	n (%)
Treatment-related AEs	10 (100)
Injection-site reaction	10 (100)
Diffuse hyperpigmentation of the skin	10 (100)
Nausea/vomiting	7 (70)
Serious AEs[a]	4 (40)
Serious treatment-related AEs	0
Treatment-related AEs leading to discontinuation	0
AEs leading to death	0

- There were no reported cardiovascular AEs related to setmelanotide
- There were no AEs or serious AEs that led to treatment discontinuation or death
- Setmelanotide was not associated with significant changes to blood pressure or heart rate
  - Diastolic blood pressure: 73.13 (baseline) to 71.50 (~1 year) mm Hg
  - Systolic blood pressure: 111.57 (baseline) to 109.83 (~1 year) mm Hg
  - Heart rate: 81.03 (baseline) to 75.37 (~1 year) beats/min

[a]Five serious AEs occurred in 4 participants, including depression, major depression, acute adrenocortical insufficiency, pneumonia, and pleurisy.

AE, adverse event; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

Conclusion

Setmelanotide reduced hunger and body weight and was well tolerated in individuals with POMC or PCSK1 deficiency obesity

- In this phase 3 study, 80% of participants achieved the primary endpoint of ≥10% weight loss from baseline at ~1 year from therapeutic dose
- Setmelanotide was associated with clinically meaningful weight loss and reduction in “most hunger” score
  - Mean change in body weight was -25.4% and mean weight loss was 31.9 kg
  - Withdrawal from setmelanotide during the 4-week placebo phase was associated with increases in weight and “most hunger” score
- Setmelanotide was generally well tolerated, and there were no AEs or serious AEs associated with setmelanotide that led to treatment discontinuation

AE, adverse event; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

Future Directions

- This study is one of two phase 3 trials supporting the potential use of setmelanotide for the treatment of early-onset severe obesity and hyperphagia
  - The second phase 3 trial supports the potential use of setmelanotide in individuals with LEPR deficiency obesity
  - The results from this study support further evaluation of setmelanotide in other disorders resulting from variants in the central melanocortin pathway, causing impaired MC4R activation

LEPR, leptin receptor; MC4R, melanocortin 4 receptor.