Effects of Setmelanotide in Patients With POMC, PCSK1, or LEPR Heterozygous Deficiency Obesity in a Phase 2 Study

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Disclosures

- SF has no conflicts of interest to report
- JM reports research funding from Rhythm Pharmaceuticals, Inc.
- OO is an employee of and stockholder in Rhythm Pharmaceuticals, Inc.
- GY is an employee of and stockholder in Rhythm Pharmaceuticals, Inc.
- MS is an employee of and stockholder in Rhythm Pharmaceuticals, Inc.
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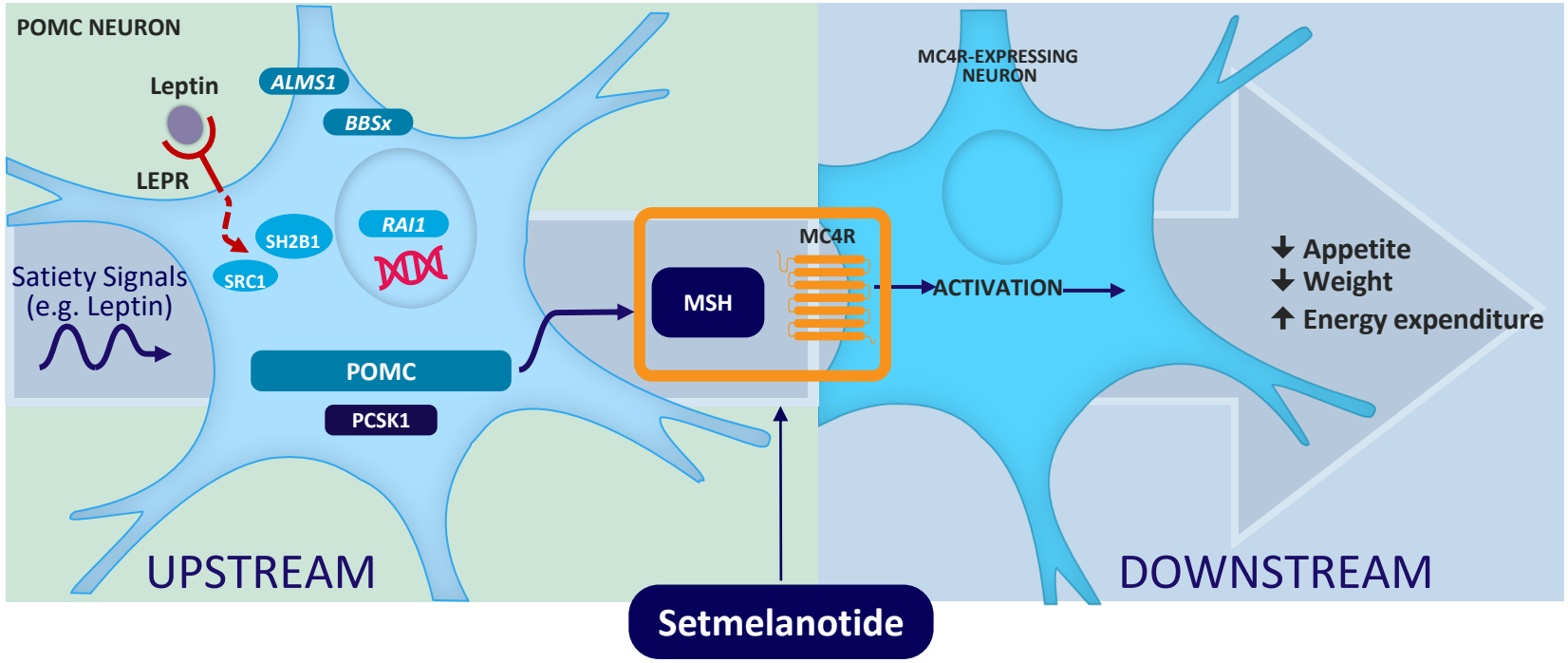
Background

- Heterozygous mutations in *POMC*, *PCSK1*, or *LEPR* can cause obesity due to partial insufficiency in the MC4R pathway[1,2]

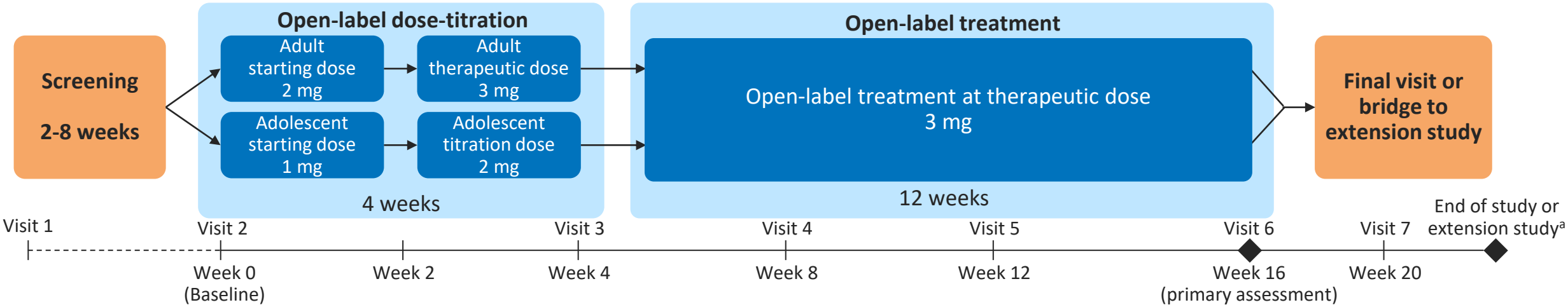


- Setmelanotide is an MC4R agonist being investigated for chronic weight management in individuals with rare genetic diseases of obesity caused by impairment of the MC4R pathway[3]

MC4R, melanocortin 4 receptor.

1. Farooqi et al. *Diabetes*. 2006;55:2549-2553. **2.** Huvenne et al. *J Clin Endocrinol Metab.* 2015;100:E757-E766. **3.** Clément et al. *Lancet Diabetes Endocrinol.* 2020;8:960-970.

Phase 2 Basket Study Design to Evaluate Response at 3 Months on Therapy



Key inclusion criteria

- *POMC*/*PCSK1*/*LEPR* heterozygous genotype
- Age ≥6 years
- Obesity
  - BMI ≥30 kg/m^2 (≥16 years of age)
  - BMI ≥95th percentile for age and sex (6–15 years of age)

Key exclusion criteria

- Gastric bypass surgery within the previous 6 months
- Any gastric bypass surgery resulting in >10% weight loss

Primary endpoint

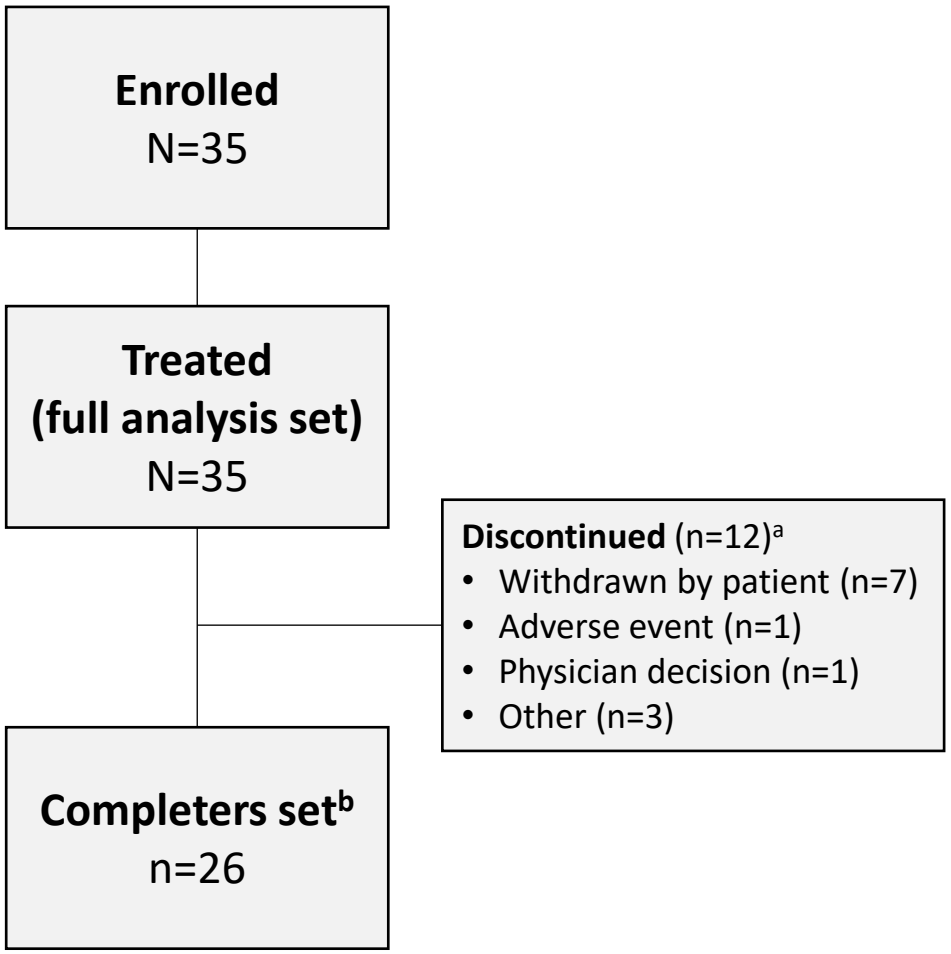
- The proportion of participants who achieve at least 5% body weight reduction from baseline at 3 months of treatment with setmelanotide

Secondary endpoint

- Hunger scores
- Adverse events

[a]Final visit at week 20 for participants not enrolling in a separate extension study.
BMI, body mass index.

Disposition and Baseline Demographics



Baseline characteristics	Full analysis set (N=35)
Age at trial enrollment, years	
Mean (SD)	39.5 (17.6)
Range	15.0–68.0
Sex, %	
Female	68.6
Male	31.4
Weight, lbs	
Mean (SD)	315.9 (65.7)
Range	210.8–459.4
Weight, kg	
Mean (SD)	143.3 (29.8)
Range	95.6–208.4
BMI, kg/m^2	
Mean (SD)	50.3 (9.4)
Range	34.7–79.1

[a]For some patients who discontinued, data are available between 60 and 120 days. [b]All participants in the full analysis set who have nonmissing data collected at least once between days 60 and 120.
SD, standard deviation.

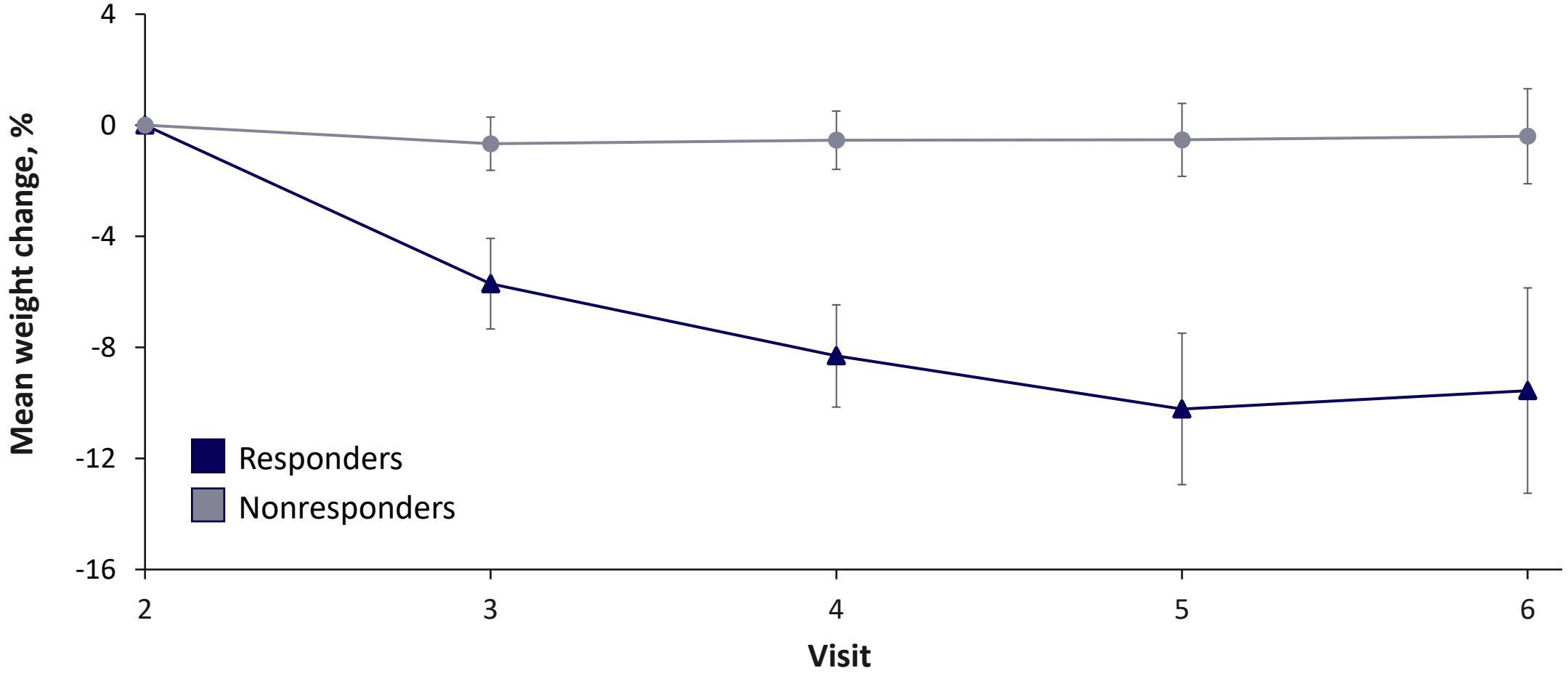
One-Third of Participants Responded to Setmelanotide

34.3% of participants (12/35) achieved the threshold of ≥5% weight loss from baseline at Month 3[a]

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight Overall (N=35)	**143.3 kg** (29.8)	**138.1 kg** (30.7)	**–3.7** (5.6)
Mean (SD) body weight Responders (n=12)	**144.7 kg** (32.6)	**130.6 kg** (33.5)	**–10.1** (4.4)

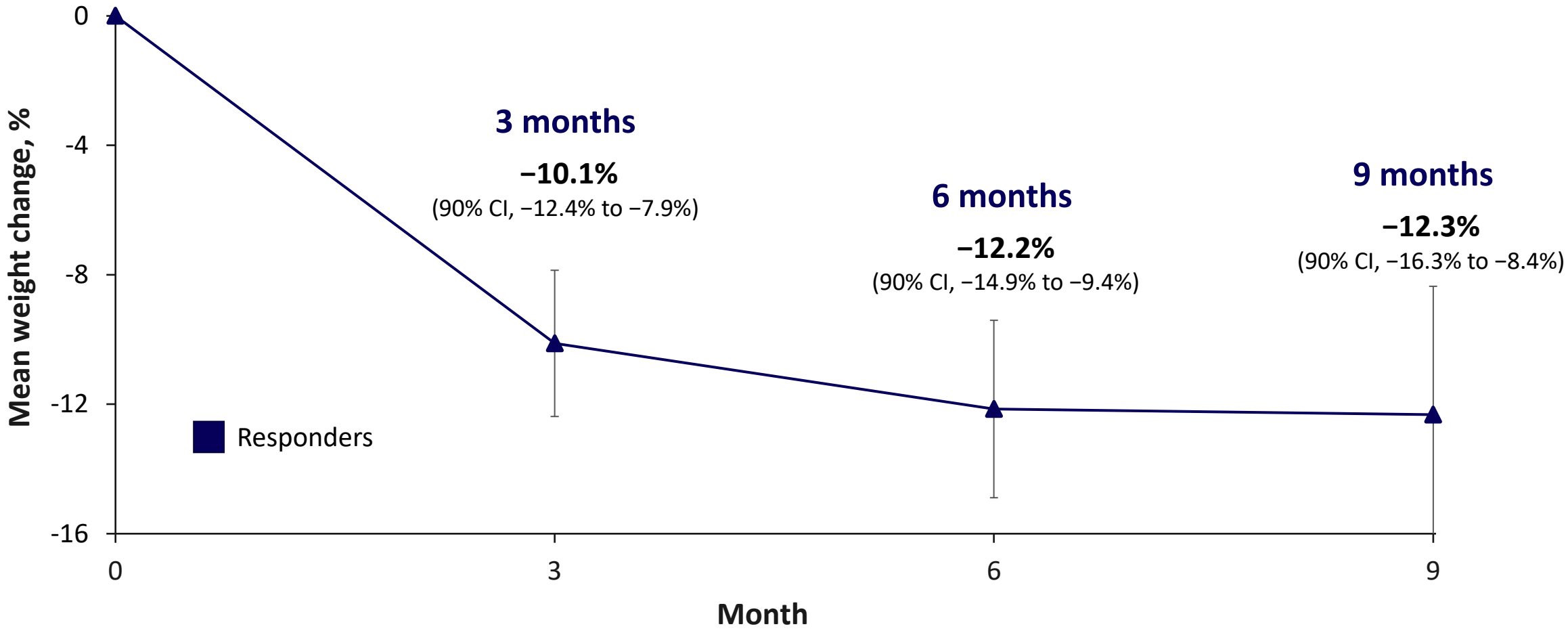
A responder was defined as having ≥5% weight loss from baseline at Month 3.
[a]Data include 6 participants who withdrew early, last observed value carried forward, as of December 17, 2020.
SD, standard deviation.

Setmelanotide Treatment Resulted in Decreased Body Weight



A responder was defined as having ≥5% weight loss from baseline at Month 3. Data as of December 17, 2020; error bars are the 90% confidence interval.

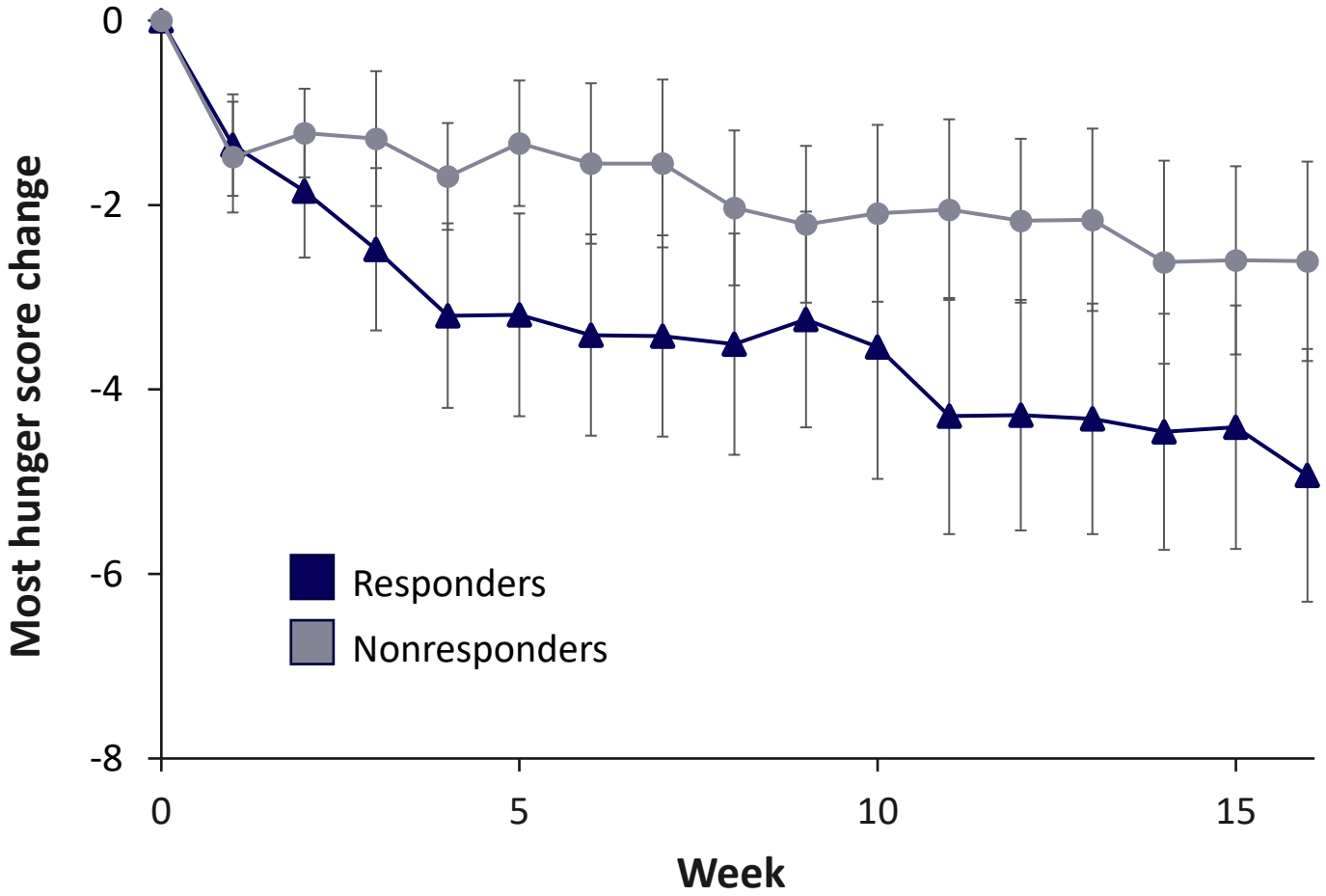
Responses to Setmelanotide Were Maintained Through 6 and 9 Months



A responder was defined as having ≥5% weight loss from baseline at Month 3. Data as of December 17, 2020, for month 3 and as of February 23, 2021, for months 6 and 9; error bars are the 90% CI.
CI, confidence interval.

Setmelanotide Treatment Resulted in Decreased Hunger Scores

	Mean change in most hunger score at Month 3
Responders (n=12)	–4.4 (90% CI –5.7, –3.2)
Nonresponders (n=23)	–2.3 (90% CI –3.2, –1.5)



A responder was defined as having ≥5% weight loss from baseline at Month 3. Data as of December 17, 2020; error bars are the 90% CI.
CI, confidence interval.

Weight Loss Was Observed Across Genotypes

ACMG subgroups	Responders, n (%)	Nonresponders, n (%)
Pathogenic/Likely pathogenic (n=8)	4 (50.0)	4 (50.0)
Variant of uncertain significance (n=19)	4 (21.1)	15 (78.9)
PCSK1 N221D (n=8)	4 (50.0)	4 (50.0)

A responder was defined as having ≥5% weight loss from baseline at Month 3. Data as of December 17, 2020.
ACMG, American College of Medical Genetics.

Setmelanotide Was Generally Well Tolerated

	n (%)
Treatment-related AEs	35 (94.6)
Serious AEs	1 (2.7)
Serious treatment-related AEs	0
AEs leading to drug discontinuation	7 (18.9)
AEs leading to death	0

- 1 participant had serious AEs of acute myocardial infarction and gastrointestinal hemorrhage that were considered unrelated to setmelanotide
- 2 additional cardiac AEs were reported; extrasystoles (n=1) and palpitations (n=1)

	n (%)
Treatment-emergent AEs occurring in ≥15% of participants	
Skin hyperpigmentation	19 (51.4)
Nausea	18 (48.6)
Injection site pruritis	14 (37.8)
Injection site erythema	12 (32.4)
Fatigue	10 (27.0)
Headache	6 (16.2)
Cough	6 (16.2)
Insomnia	6 (16.2)

AE, adverse event.

Summary and Conclusions

- Overall, ~35% of participants with obesity due to *POMC*, *PCSK1*, or *LEPR* heterozygous deficiency responded with ≥5% weight loss at Month 3
  - Responders had continued weight loss at 6 and 9 months (12.2%–12.3%)
- There was a clear separation between responders and nonresponders in terms of weight loss and changes in hunger scores
- The adverse event profile for setmelanotide was consistent with what has been previously described
- Setmelanotide may be a viable treatment option for some participants with obesity due to *POMC*, *PCSK1*, or *LEPR* heterozygous deficiency

Key References

- Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020;8(12):960-970.
- Farooqi IS, Drop S, Clements A, et al. Heterozygosity for a POMC-null mutation and increased obesity risk in humans. *Diabetes*. 2006;55(9):2549-2553.
- Farooqi IS, Wangensteen T, Collins S, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med*. 2007;356:237-247.