Efficacy and Safety Results of a Phase 2 Trial of Setmelanotide in Obesity Due to *SH2B1* Variants and 16p11.2 Deletion Syndrome

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Conflict of Interest

Name: Cecilia Scimia

☐ I have the following potential conflicts of interest to report:

- ☐ Research contracts
- ☐ Consulting
- ✓ Employment in the industry
- ✓ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ I declare that I have no potential conflict of interest.

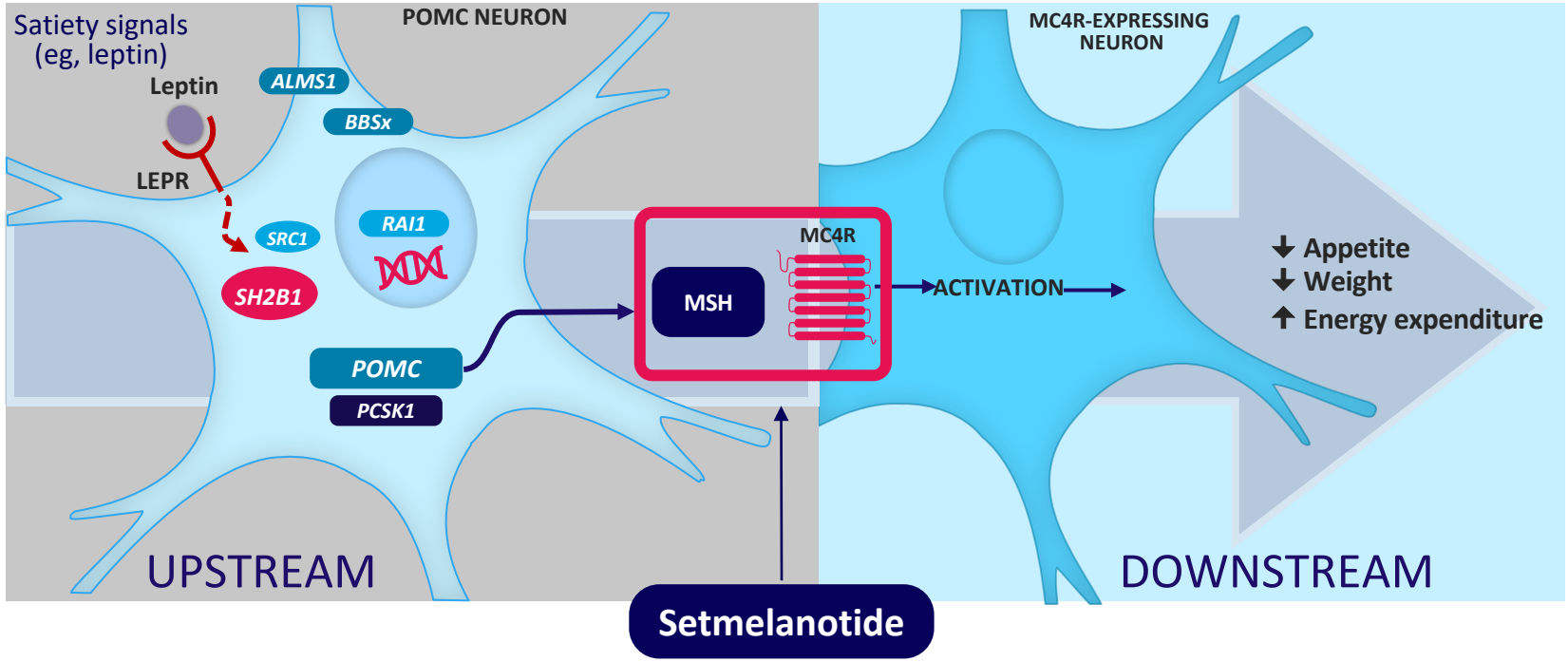
Disclosures

This study was sponsored by Rhythm Pharmaceuticals, Inc.

Background

- Leptin is released by adipose tissue and stimulates the MC4R pathway in the hypothalamus to signal satiety and increase energy expenditure[1]

- SH2B1 is involved in the MC4R pathway and promotes leptin signaling through Jak2[2]
- Variants in *SH2B1* or a 220–kilobase pair distal deletion of chromosome 16p11.2, including *SH2B1*, are associated with early-onset, severe obesity and hyperphagia[3,4]

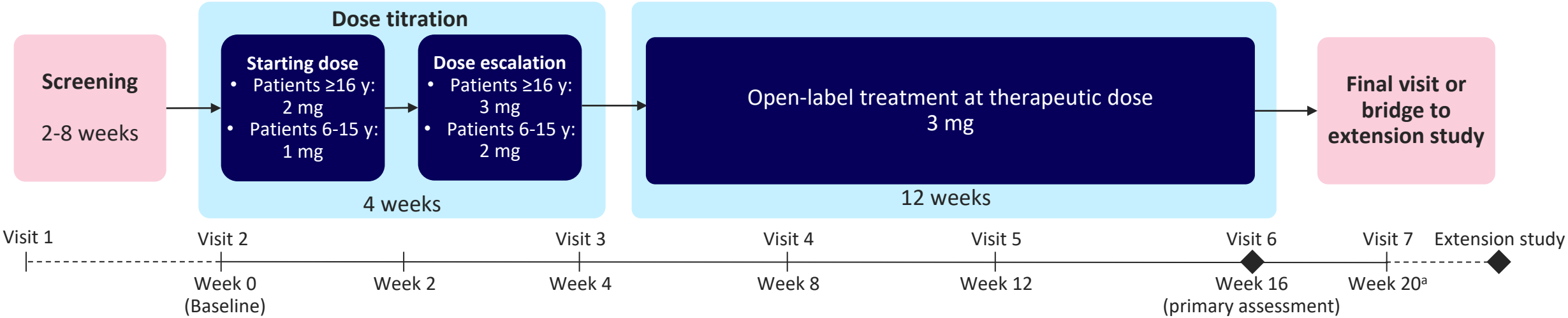


- Setmelanotide is an MC4R agonist being investigated for weight loss and hunger reduction in individuals with rare genetic diseases of obesity caused by impairment of the MC4R pathway[5]

Jak2, Janus kinase 2; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; SH2B1, SH2B adaptor protein 1.

1. Huvenne et al. *Obes Facts*. 2016;9:158-173. **2.** Perrone et al. *Ital J Pediatr*. 2010;36:43. **3.** Doche et al. *J Clin Invest*. 2012;122:4732-4736. **4.** Bochukova et al. *Nature.* 2010;463:666-670. **5.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03013543. Updated June 2, 2021. Accessed July 13, 2021.

Phase 2 Study Design to Evaluate Response to Setmelanotide at Month 3



Key inclusion criteria

- *SH2B1* variant or distal deletion of chromosome 16p11.2, including *SH2B1*[1]
- 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

- >2% weight loss from a recent intensive diet or exercise regimen
- Gastric bypass surgery within the previous 6 months
- Any gastric bypass surgery resulting in >10% weight loss

Primary endpoint

- The proportion of patients who achieve ≥5% body weight reduction from baseline at ~3 months of treatment with setmelanotide

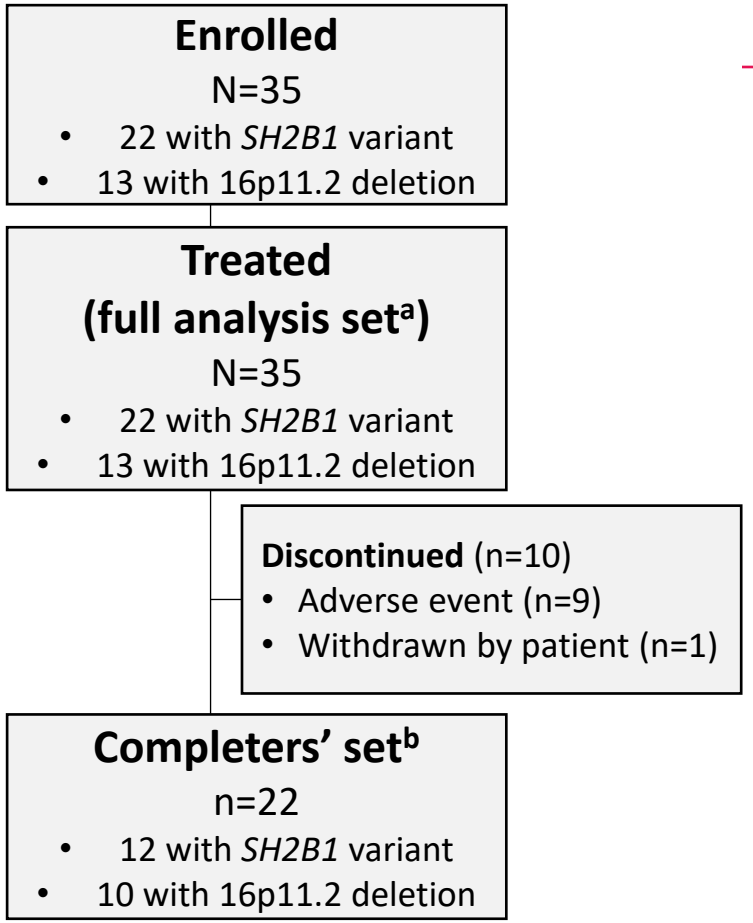
Secondary endpoints

- Hunger scores
- Adverse events

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

1. Bochukova et al. *Nature.* 2010;463:666-670.

Disposition and Baseline Demographics

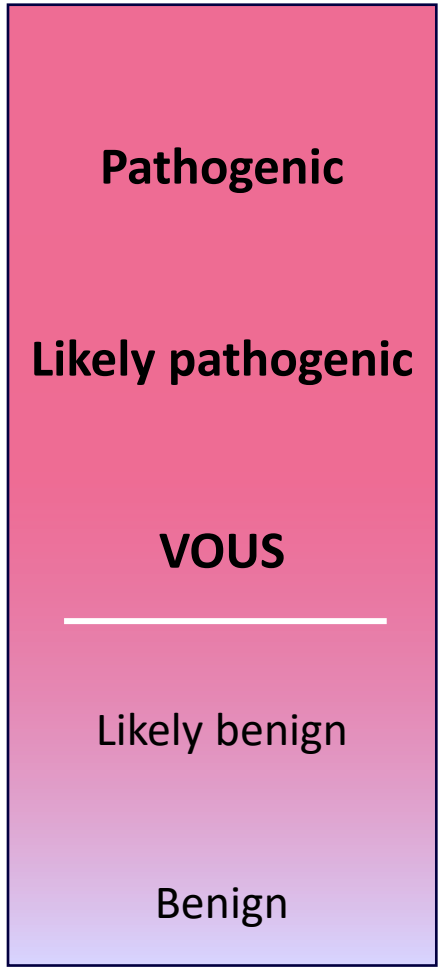


Baseline characteristics	Full analysis set (N=35)
Age at trial enrollment, years	
Mean (SD)	31.1 (17.3)
Range	8.0–67.0
Sex, %	
Female	68.6
Male	31.4
Mean (SD) body weight, kg	127.4 (38.8)
Mean (SD) [n] body weight in those ≥18 years old, kg	139.7 (35.4) [22]
Mean (SD) BMI, kg/m^2	47.2 (12.8)
Mean (SD) [n] BMI Z score in those <18 years old	3.6 (0.6) [13]

- Patients were enrolled from August 2019 and the study is ongoing

[a]Patients who received ≥1 dose of study drug and completed baseline assessment. [b]All patients in the full analysis set who have nonmissing data collected at least once between Days 60 and 120.
BMI, body mass index; SD, standard deviation.

Patient ACMG Variant Classification



Baseline characteristics	Full analysis set (N=35)
SH2B1 variant	
Pathogenic/Likely pathogenic, n (%)	0
VOUS, n (%)	22 (100)
16p11.2 deletion, including *SH2B1*	
Pathogenic/Likely pathogenic, n (%)	12 (92)
VOUS, n (%)	0
Not available	1 (8)

ACMG, American College of Medical Genetics; VOUS, variant of uncertain significance.

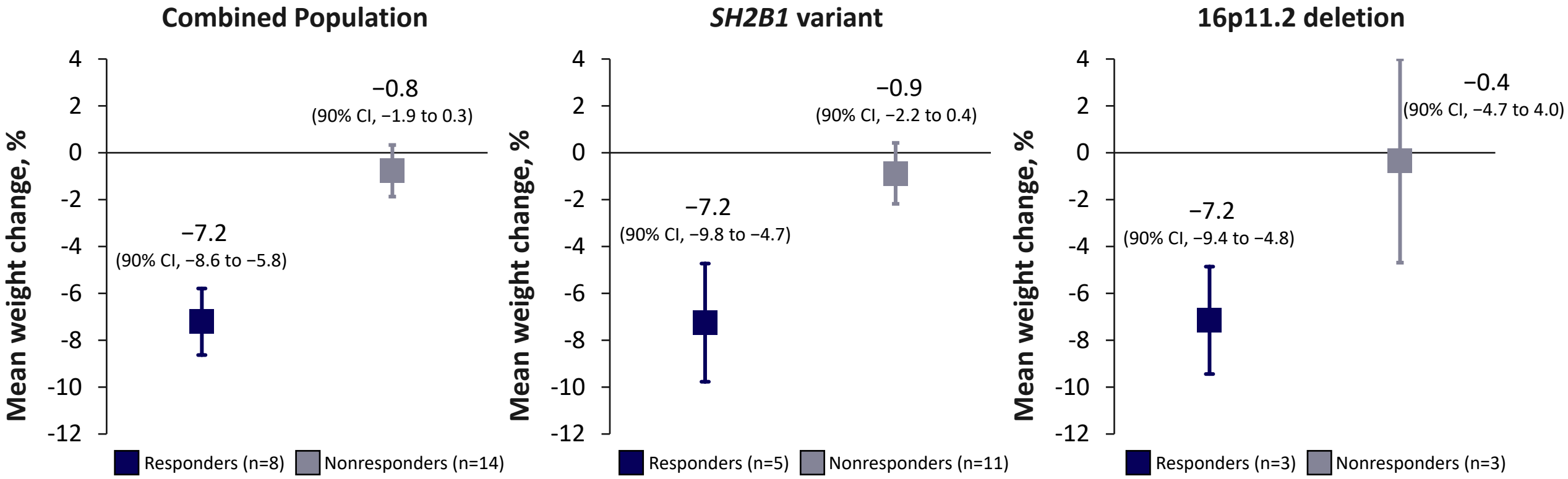
More Than One-Third of Patients Respond to Setmelanotide Treatment

42.9% of patients (15/35) have achieved the threshold of ≥5% weight loss or ≥0.15 reduction in BMI Z score from baseline at Month 3

Proportion of patients	*SH2B1* variant	16p11.2 deletion	Overall
≥5% weight loss in those ≥18 years old, n/N (%)	5/16 (31.3)	3/6 (50.0)	8/22 (36.4)
≥0.15 reduction in BMI Z score in those <18 years old, n/N (%)	5/6 (83.3)	2/7 (28.6)	7/13 (53.8)
Overall	10/22 (45.5)	5/13 (38.5)	15/35 (42.9)

Full analysis set reported. In the Completers' set, 59.1% of patients (13/22) were considered responders, including 53.8% of patients (7/13) ≥18 years old and 66.6% of patients (6/9) <18 years old. A responder was defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old.
BMI, body mass index.

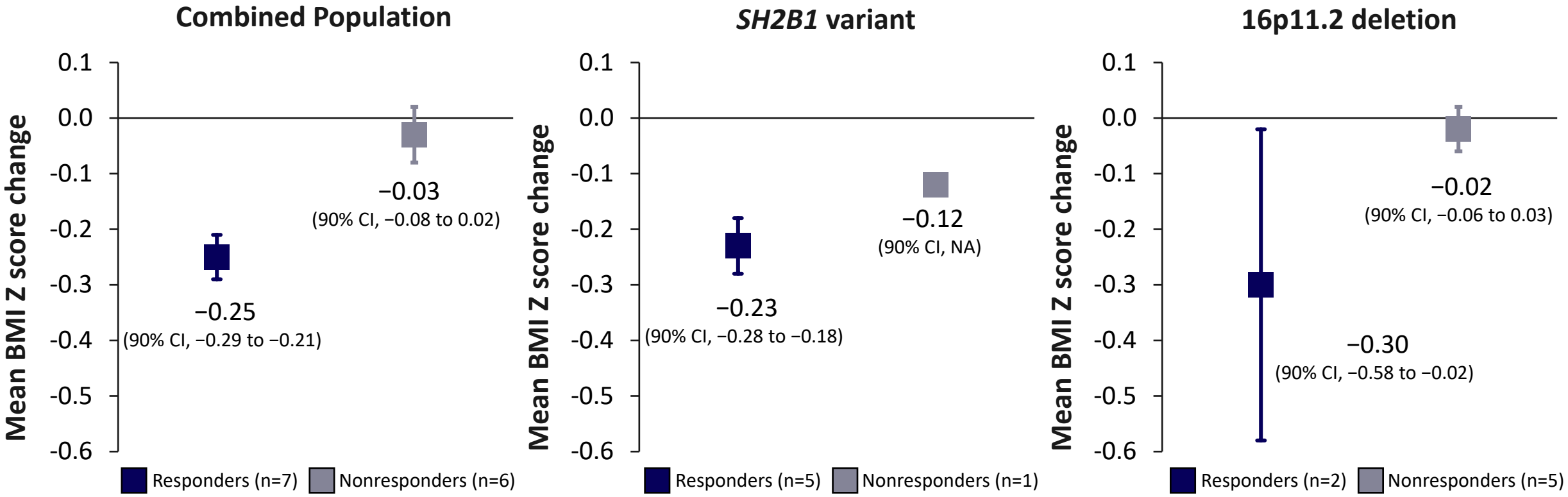
Setmelanotide Treatment Decreases Body Weight in Adults



- For the combined population, mean (SD) overall body weight change from baseline of −3.1% (3.9%; n=22)

Full analysis set reported. In the Completers' set, in the combined population, mean percent weight change for responders was −7.3% (90% CI, −9.0% to −5.7%; n=7) and for nonresponders was −0.2% (90% CI, −2.8% to 2.4%; n=6). A responder was defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI.
CI, confidence interval; SD, standard deviation.

Setmelanotide Treatment Decreases BMI Z Score in Children and Adolescents



- For the combined population, mean (SD) overall BMI Z score change from baseline of −0.15 (0.13; n=13)

Full analysis set reported. In the Completers' set, in the combined population, mean BMI Z score change for responders was −0.25 (90% CI, −0.30 to −0.19; n=6) and for nonresponders was −0.05 (90% CI, −0.16 to 0.07; n=3). A responder was defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI.
BMI, body mass index; CI, confidence interval; NA, not available; SD, standard deviation.

Setmelanotide Is Generally Well Tolerated

	n (%)
Treatment-related AEs	32 (91.4)
Serious AEs	1 (2.9)
Serious treatment-related AEs	0
AEs leading to drug discontinuation	9 (25.7)
AEs leading to death	0

- One serious AE of melanocytic nevus has occurred in an adult patient, for which melanoma was excluded, which was considered **not treatment related**

	n (%)
Treatment-emergent AEs occurring in ≥15% of patients	
Skin hyperpigmentation	25 (71.4)
Nausea	17 (48.6)
Headache	13 (37.1)
Injection site pruritus	9 (25.7)
Injection site erythema	6 (17.1)
Injection site pain	6 (17.1)
Vomiting	6 (17.1)
Melanocytic nevus	6 (17.1)

Safety analysis set, defined as all patients who received ≥1 dose of study drug, reported.
AE, adverse event.

Summary and Conclusions

- Patients with *SH2B1* variants or 16p11.2 deletion syndrome have early-onset, severe obesity[1,2]
  - In this trial, patients have severe obesity despite a relatively young age
- Overall, 43% of patients with obesity due to *SH2B1* variants or 16p11.2 deletion have responded with ≥5% weight loss or ≥0.15 reduction in BMI Z score after 3 months
  - Response rates are similar in those with *SH2B1* variants (46%) and 16p11.2 deletion (38%)
  - Response rates are somewhat higher in those aged <18 years (54%) compared with ≥18 years (36%)
- There is a clear separation between responders and nonresponders in terms of weight loss or change in BMI Z score
- No new safety events have emerged
- A 3-month initial treatment period may be useful to identify individuals with setmelanotide-responsive variants involving *SH2B1* for potential long-term treatment, as will be evaluated in the upcoming Phase 3 EMANATE trial

BMI, body mass index.

1. Doche et al. *J Clin Invest*. 2012;122:4732-4736. **2.** Bochukova et al. *Nature.* 2010;463:666-670.