A Phase 2 Trial of the Melanocortin-4 Receptor Agonist Setmelanotide in Obesity Due to SRC1 Insufficiency: Body Weight, Body Mass Index Z Score, and Safety Results

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ESPE 2021 Online Conflict of Interest

Name: Sadaf Farooqi

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

- SRC1 is a transcriptional coactivator that together with STAT3 stimulates *POMC* expression as part of the MC4R pathway in mice[2]

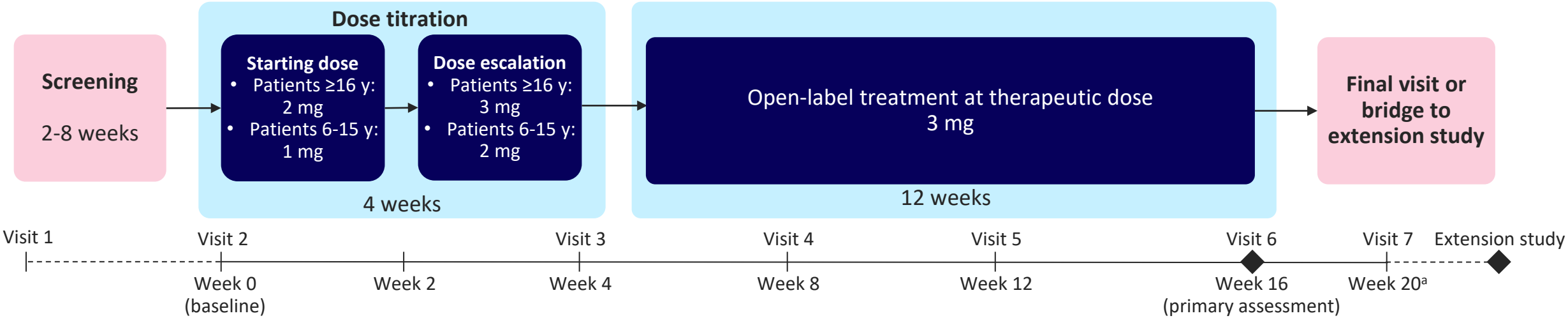
- Certain heterozygous variants in *SRC1* are associated with early-onset, severe obesity[2]

- Setmelanotide, an MC4R agonist, is being investigated in a basket study of populations with rare variants in different genes in the MC4R pathway who have early-onset, severe obesity and hyperphagia[3]

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; SRC1, steroid receptor coactivator 1; STAT3, signal transducer and activator of transcription 3.

1. Huvenne et al. *Obes Facts*. 2016;9:158-173. **2.** Yang et al. *Nat Commun*. 2019;10:1718. **3.** 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

- SRC1 insufficiency
- 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

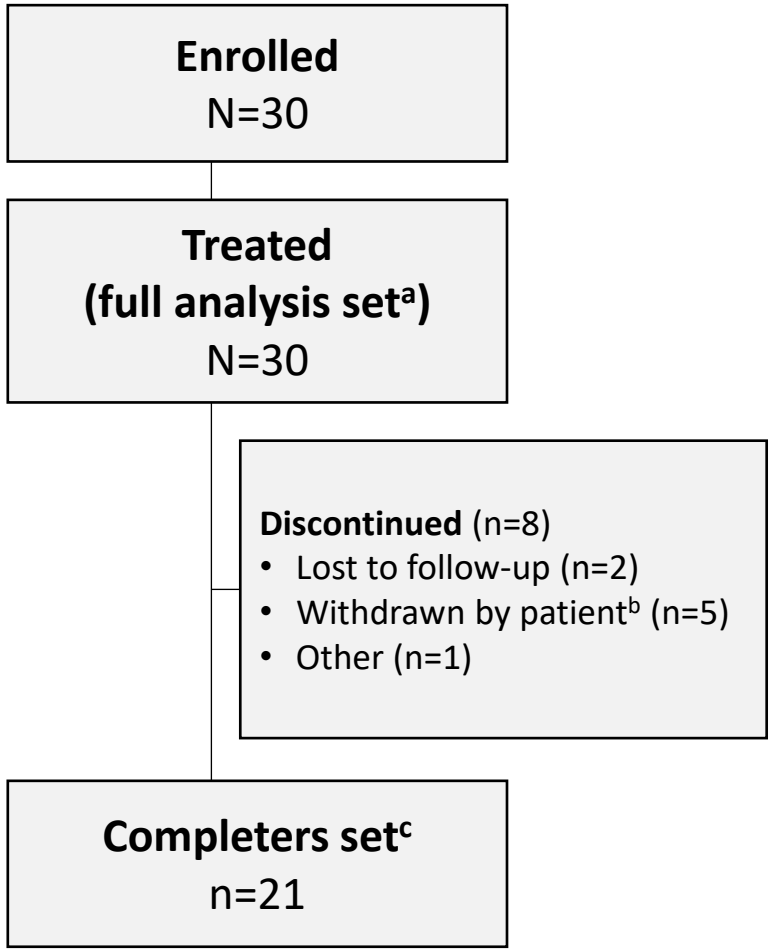
- The proportion of patients who achieve ≥5% body weight reduction from baseline at ~3 months of treatment with setmelanotide

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; SRC1, steroid receptor coactivator 1.

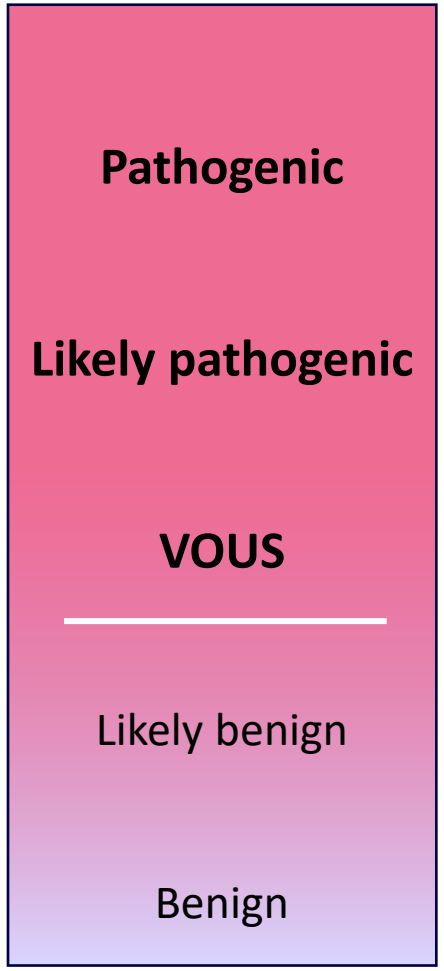
Disposition and Baseline Demographics



Baseline characteristics[d]	Full analysis set (N=30)
Age at trial enrollment, years	
Mean (SD)	30.6 (17.5)
Range	9.0–66.0
Sex, %	
Female	80.0
Male	20.0
Mean (SD) body weight, kg	122.6 (34.2)
Mean (SD) [n] body weight in those ≥18 years old, kg	139.7 (25.1) [20]
Mean (SD) BMI, kg/m^2	45.4 (11.3)
Mean (SD) [n] BMI Z score in those <18 years old	3.0 (0.6) [10]

[a]Patients who received ≥1 dose of study drug and completed baseline assessment. [b]Reasons for treatment discontinuation include not wanting to take injections, schedule conflict, adverse event, lack of efficacy, and family hardship due to the COVID-19 pandemic. [c]All patients in the full analysis set who have nonmissing data collected at least once between Days 60 and 120. [d]No patients reported cognitive impairment.
BMI, body mass index; SD, standard deviation.

Patient ACMG Variant Classification



Baseline characteristics	Full analysis set (N=30)
Pathogenic/Likely pathogenic, n (%)	0
VOUS, n (%)	30 (100)

- Subgroup analyses based on ACMG classification are not available at this time

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

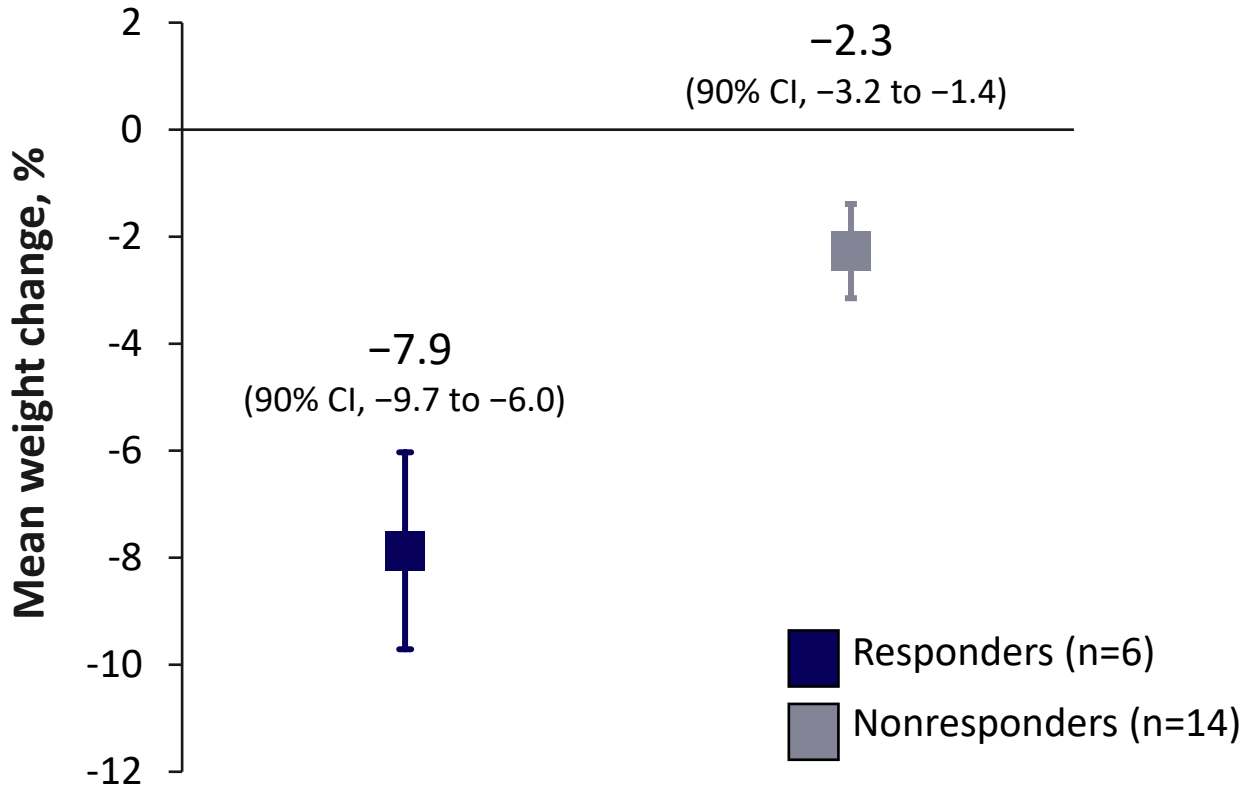
Approximately One-Third of Patients Respond to Setmelanotide Treatment

30% of patients (9/30) have achieved the threshold of ≥5% weight loss or ≥0.15 reduction in BMI Z score from baseline at Month 3

	Responders
≥5% weight loss in those ≥18 years old, n/N (%)	**6/20 (30)**
≥0.15 reduction in BMI Z score in those <18 years old, n/N (%)	**3/10 (30)**

Full analysis set reported. In the Completers' set, 33.3% of patients (7/21) were considered responders, including 33.3% of patients (3/9) ≥18 years old and 33.3% of patients (4/12) <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.

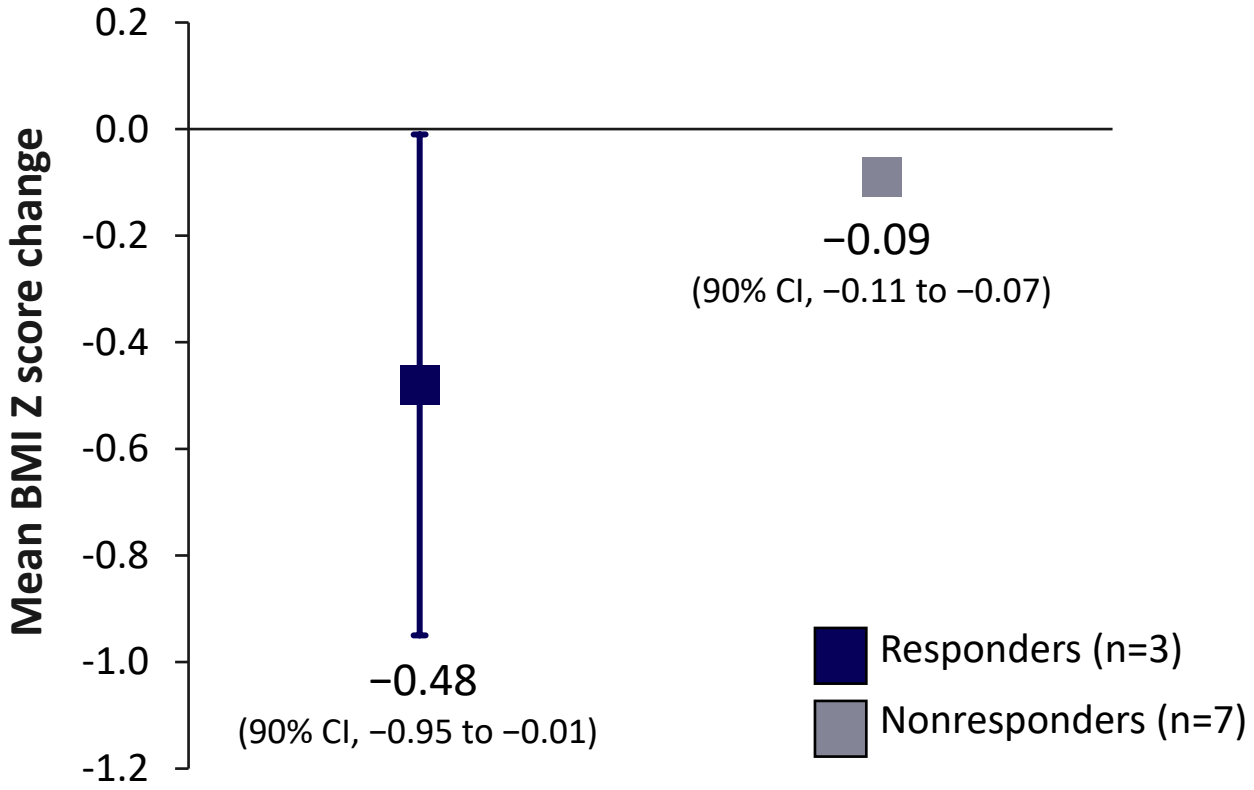
Setmelanotide Treatment Decreases Body Weight in Adults



- Mean (SD) overall body weight change from baseline of −4.0% (3.3%; n=20)

Full analysis set reported. In the Completers' set, mean percent weight change for responders was −8.7% (90% CI, −11.4% to −6.0%; n=4) and for nonresponders was −2.6% (90% CI, −3.8% to −1.3%; n=8). 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



- Mean (SD) overall BMI Z score change from baseline of −0.21 (0.23; n=10)

Full analysis set reported. In the Completers' set, mean BMI Z score change for responders was −0.48 (90% CI, −0.95 to −0.01; n=3) and for nonresponders was −0.09 (90% CI, −0.11 to −0.07; 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.
BMI, body mass index; CI, confidence interval.

Setmelanotide Is Generally Well Tolerated

	n (%)
Treatment-related AEs	26 (86.7)
Serious AEs	0
Serious treatment-related AEs	0
AEs leading to drug discontinuation	1 (3.3)
AEs leading to death	0

- One patient has discontinued setmelanotide because of AEs (including nausea, dizziness, increased libido, and increased vaginal discharge)

	n (%)
Treatment-emergent AEs occurring in ≥15% of patients	
Skin hyperpigmentation	20 (66.7)
Nausea	11 (36.7)
Injection site bruising	9 (30.0)
Injection site erythema	7 (23.3)
Headache	6 (20.0)
Injection site pruritis	6 (20.0)

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

Summary and Conclusions

- SRC1 insufficiency can lead to early-onset, severe obesity[1]
  - In this trial, patients with SRC1 insufficiency have severe obesity at a relatively young age
- Overall, 30% of patients with obesity due to SRC1 insufficiency have responded to setmelanotide after 3 months
  - Response rates are similar in those aged ≥18 years (30%) and those <18 years (30%)
- 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 SRC1 for potential long-term treatment, as will be evaluated in the upcoming Phase 3 EMANATE trial

BMI, body mass index; MC4R, melanocortin-4 receptor; SRC1, steroid receptor coactivator 1.

1. Yang et al. *Nat Commun*. 2019;10:1718.