Effects of Setmelanotide on Obesity, Hunger, and Safety in SRC1 Insufficiency: a Phase 2 Trial

Sadaf Farooqi,[1] Michal Ben-Ami,[2] Eirini Kostopoulou,[3] Gabriel Á. Martos-Moreno,[4] Shana McCormack,[5] Elif A. Oral,[6] Orit Pinhas-Hamiel,[2] Bessie E. Spiliotis,[3] Olga Ohayon,[7] Cecilia Scimia,[7] Guojun Yuan,[7] Murray Stewart,[7] Jesús Argente[4,8]

[1]Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK; [2]Pediatric Endocrinology & Diabetes Unit, Sheba Medical Center, Ramat Gan, Israel; [3]Division of Pediatric Endocrinology & Diabetes, University of Patras School of Medicine, Patras, Greece; [4]Universidad Autónoma de Madrid, Departments of Pediatrics & Pediatric Endocrinology, Hospital Infantil Universitario Niño Jesús, CIBER "Fisiopatología de la Obesidad y Nutrición" (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain; [5]Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Elizabeth Weiser Caswell Diabetes Institute, Ann Arbor, MI, USA; [7]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [8]IMDEA Food Institute, Madrid, Spain

Presenting Author:
Sadaf Farooqi
isf20@medschl.cam.ac.uk

Summary

- 3 months of setmelanotide reduced hunger and body weight in patients with steroid receptor coactivator 1 (SRC1) insufficiency and may be a beneficial long-term treatment

Introduction

- Hyperphagia and early-onset, severe obesity may signify a genetic cause, such as impaired signaling through the melanocortin-4 receptor (MC4R) pathway[1]
- SRC1 is a transcriptional coactivator that stimulates proopiomelanocortin expression in mice as part of the MC4R pathway[2]
- Some heterozygous variants in *SRC1* are associated with early-onset, severe obesity[2]
- We hypothesized that 3-month treatment with the specific MC4R agonist setmelanotide would identify a subgroup of individuals with variants in *SRC1* who may benefit from longer-duration targeted therapy

Objective

- To investigate the effect of setmelanotide treatment on individuals with obesity due to SRC1 insufficiency

Methods

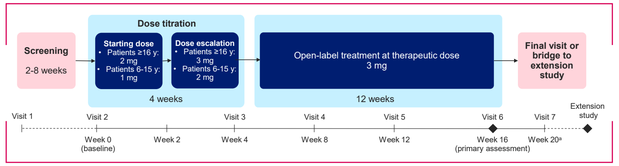
Study Design

- This ongoing Phase 2 uncontrolled study (NCT03013543) investigated setmelanotide treatment in individuals aged ≥6 years with SRC1 insufficiency and obesity
  - Obesity was defined as body mass index (BMI) ≥95th percentile for those aged 6–15 years or BMI ≥30 kg/m^2 for those aged ≥16 years
  - Relevant exclusion criteria included >2% weight loss from diet or exercise regimen within 2 months, >10% durable weight loss from prior gastric bypass surgery or gastric bypass surgery within 6 months, and any use of obesity drugs within 3 months
- Following dose titration, participants received open-label treatment until Month 3 (Figure 1)

Endpoints and Assessments

- The primary endpoint was the proportion of patients who achieve ≥5% body weight reduction from baseline at Month 3 of treatment with setmelanotide
- The proportion of patients who achieved ≥0.15 reduction in BMI Z score (for those aged <18 years old) or ≥5% weight loss (for those ≥18 years old) was also assessed as an exploratory endpoint at Month 3
- As a secondary endpoint, patients ≥12 years old reported their own hunger daily through questionnaires
  - Hunger scores were reported on a numerical scale ranging from 0 to 10, with 0 being not hungry at all and 10 being the hungriest possible
- Efficacy data are from the full analysis set, defined as all patients with ≥1 dose of study drug and baseline data, unless stated otherwise
  - The safety analysis set was defined as all patients who received ≥1 dose of study drug
  - The completers' set was defined as all patients in the full analysis set who had weight data collected ≥1 time between Day 60 and 120

Figure 1. Study design.



[a]Final visit at Week 20 for patients not enrolling in a separate extension study.

Results

Patient Disposition and Demographics

- 30 patients were enrolled and received setmelanotide (Table 1)
- 8 patients discontinued treatment
  - 2 were lost to follow-up, 5 withdrew for reasons including not wanting to take injections, schedule conflict, adverse event (AE), lack of efficacy, and family hardship due to the COVID-19 pandemic, and 1 discontinued for other reasons

Table 1. Patient Demographics

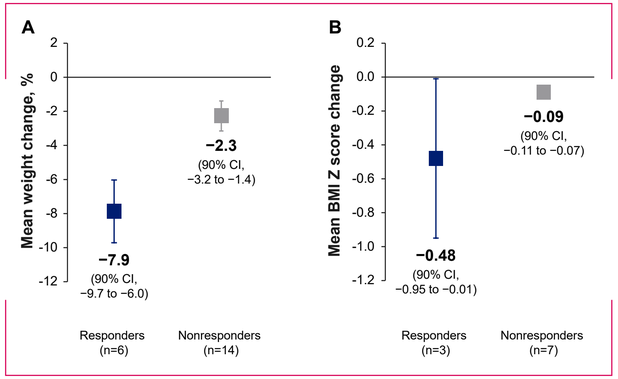
	Full analysis set (N=30)
Age, mean (SD) [range], years	30.6 (17.5) [9.0–66.0]
Female, n (%)	24 (80)
Race, n (%)	
White	23 (76.7)
Black or African American	5 (16.7)
Other	2 (6.7)
Ethnicity, n (%)	
Hispanic or Latino	2 (6.7)
Not Hispanic or Latino	28 (93.3)
ACMG variant of uncertain significance	30 (100)
Body weight, mean (SD), kg	122.6 (34.2)
Body weight in those ≥18 years old, mean (SD) [n], kg	139.7 (25.1) [20]
BMI, mean (SD), kg/m^2	45.4 (11.3)
BMI Z score in those <18 years old, mean (SD) [n]	3.0 (0.6) [10]
"Most" hunger score in those ≥12 years old, mean (SD) [n]	7.0 (1.9) [29]

ACMG, American College of Medical Genetics; BMI, body mass index; SD, standard deviation.

Efficacy at Month 3

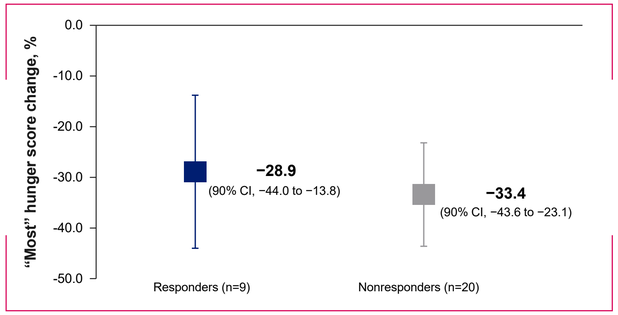
- 9 of the 30 patients (30%) achieved the primary endpoint of ≥5% body weight reduction from baseline at Month 3
- 9 of the 30 patients (30%) achieved ≥0.15 reduction in BMI Z score in those <18 years old or ≥5% weight loss in those ≥18 years old and were classified as responders
  - 3 responders were <18 years old and 6 responders were ≥18 years old
  - 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
- Mean (90% confidence interval [CI]) change in BMI Z score in patients <18 years old was −0.48 (−0.95 to −0.01; n=3) for responders versus −0.09 (−0.11 to −0.07; n=7) for nonresponders (Figure 2)
  - In the completers' set, mean (90% CI) BMI Z score change was −0.48 (−0.95 to −0.01; n=3) for responders and was −0.09 (−0.11 to −0.07; n=6) for nonresponders
- Mean (90% CI) percent weight change in patients ≥18 years old was −7.9% (−9.7% to −6.0%; n=6) for responders versus −2.3% (−3.2% to −1.4%; n=14) for nonresponders
  - In the completers' set, mean (90% CI) percent weight change was −8.7% (−11.4% to −6.0%; n=4) for responders and −2.6% (−3.8% to −1.3%; n=8) for nonresponders
- Mean (90% CI) percent reduction in "most" hunger score in participants ≥12 years old was −28.9% (−44.0% to −13.8%; n=9) for responders versus −33.4% (−43.6% to −23.1%; n=20) for nonresponders (Figure 3)

Figure 2. (**A**) Percent change in body weight (in those ≥18 years old) and (**B**) absolute change in BMI Z score (in those <18 years old) at Month 3.



Full analysis set reported. A responder was defined as having ≥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% confidence interval. BMI, body mass index.

Figure 3. Percent change in "most" hunger score (in those ≥12 years old) at Month 3.



Full analysis set reported. A responder was defined as having ≥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% confidence interval. BMI, body mass index.

Safety at Month 3

- The most common AEs were skin hyperpigmentation (66.7%) and nausea (36.7%) (Table 2)
  - 90.0% of patients reported ≥1 AE
- No serious AEs occurred
- 1 patient discontinued setmelanotide because of AEs (including nausea, dizziness, increased libido, and increased vaginal discharge)

Table 2. Treatment-Emergent Adverse Events Occurring in ≥15% of Patients[a]

	n (%)
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)

[a]Safety analysis set, defined as all patients who received ≥1 dose of study drug.

Conclusions

- In this trial, patients with SRC1 insufficiency had severe obesity despite a relatively young age
- Hunger was reduced in patients aged ≥12 years regardless of responder classification
- Body weight (in those aged ≥18 years) and BMI Z score (in those aged <18 years) response rates to setmelanotide were similar (30% for both)
- No new safety events emerged
- A 3-month initial treatment period may be useful to identify individuals with obesity due to functional variants in the MC4R pathway who respond to setmelanotide, as will be evaluated in the upcoming Phase 3 EMANATE trial

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided under the direction of the authors by Kristin French, PhD, and David Boffa, ELS, of MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

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