Setmelanotide in POMC, PCSK1, or LEPR Heterozygous Deficiency Obesity

Sadaf Farooqi, PhD[1]; Jennifer Miller, MD[2]; Olga Ohayon,[3] Guojun Yuan, PhD[3]; Murray Stewart, DM, FRCP[3]; Cecilia Scimia, MD, PhD[3]; Jack A. Yanovski, MD, PhD[4]

[1]Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK; [2]Pediatric Endocrinology, University of Florida, Gainesville, FL, USA; [3]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [4]Section on Growth and Obesity, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

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

Summary

- **Overall, ~35% of participants with obesity due to *POMC*, *PCSK1*, or *LEPR* heterozygous variants responded with ≥5% weight loss at Month 3**
- **Responders had continued weight loss at 6 and 9 months (range, 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 (AE) 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 variants**

Introduction

- Heterozygous mutations in genes encoding proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) can cause obesity due to impairment in the melanocortin-4 receptor (MC4R) pathway[1,2]
- Setmelanotide is an MC4R agonist being investigated for long-term weight management in patients with rare genetic diseases of obesity caused by MC4R pathway impairment[3]

Objectives

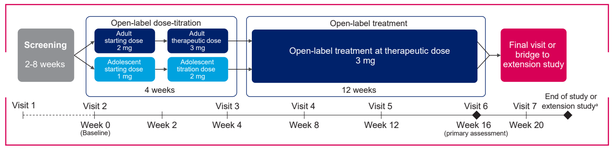
- To determine the efficacy and safety of setmelanotide in patients with partial insufficiency in the MC4R pathway due to heterozygous *POMC*, *PCSK1*, or *LEPR* variants

Methods

Study Design

- This was an open-label, single-arm, Phase 2 study of setmelanotide in participants with POMC, PCSK1, or LEPR deficiency obesity caused by heterozygous gene variants (NCT03013543)
- Participants received once-daily setmelanotide, which was titrated for 4 weeks to establish the therapeutic dosage (3 mg daily), then continued for 12 additional weeks (Figure 1)

Figure 1. Study design.



[a]Final visit at week 20 for participants not enrolling in a separate extension study.

Key Enrollment Criteria

- Inclusion criteria included *POMC/PCSK1/LEPR* heterozygous genotype, age ≥6 years, and obesity (defined as body mass index [BMI] ≥30 kg/m^2 in those ≥16 years of age or BMI ≥95th percentile for age and sex in those 6–15 years of age)
- Exclusion criteria included gastric bypass surgery within the previous 6 months or any gastric bypass surgery resulting in >10% weight loss

Key Endpoints

- The primary endpoint was mean percent change from baseline in body weight at Month 3
  - A treatment responder was defined as having ≥5% weight loss from baseline at Month 3
- Hunger scores and AEs were secondary endpoints

Results

Participant Disposition and Baseline Characteristics

- A total of 35 participants were enrolled in the study (Table 1), with 26 completing the study

Table 1. Participant Characteristics

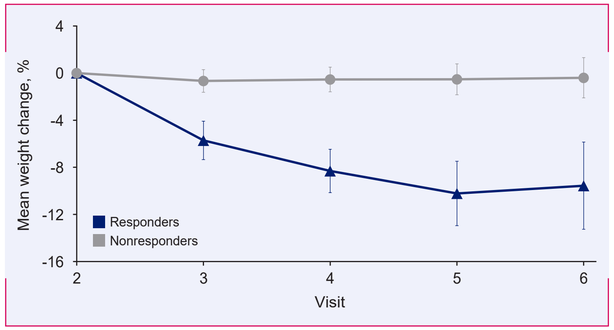
		N=35
Age at trial enrollment, years	Mean (SD)	39.5 (17.6)
	Range	15.0–68.0
Sex, %	Female	68.6
	Male	31.4
Weight, lbs	Mean (SD)	315.9 (65.7)
	Range	210.8–459.4
Weight, kg	Mean (SD)	143.3 (29.8)
	Range	95.6–208.4
BMI, kg/m^2	Mean (SD)	50.3 (9.4)
	Range	34.7–79.1

BMI, body mass index; SD, standard deviation.

Key Efficacy Outcomes

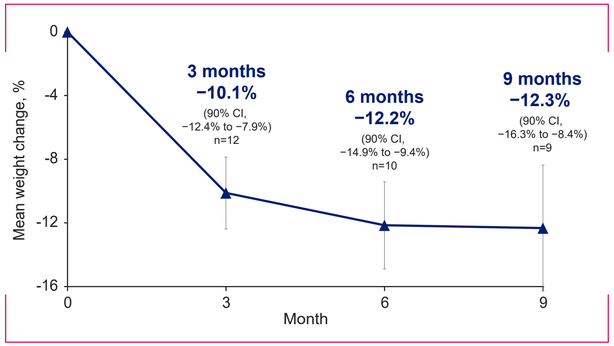
- In all patients, mean percent change in body weight from baseline to Month 3 was −3.7% (90% confidence interval [CI], −5.3% to −2.1%)
- Twelve of 35 patients (34.3%) were responders (Figure 2)
  - Mean percent change in body weight from baseline to Month 3 in responders was −10.1% (n=12); treatment response was maintained through 6 and 9 months (Figure 3)
  - Mean change in most hunger score from baseline to Month 3 in responders was −4.5 (Figure 4)

Figure 2. Mean percent change in body weight from baseline to Month 3 in all participants.



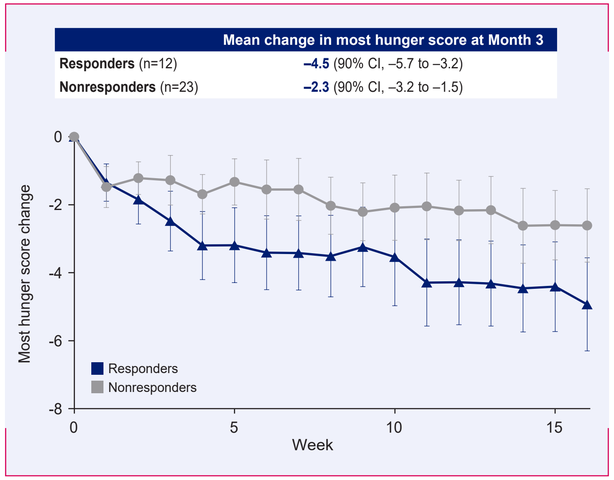
Data as of December 20, 2020; error bars are the 90% confidence interval.

Figure 3. Mean percent change in body weight from baseline to Month 9 in responders.



Data as of December 20, 2020 (for Month 3) and as of February 23, 2021 (for Months 6 and 9). Error bars are the 90% confidence interval (CI).

Figure 4. Change in most hunger score from baseline to Month 3.



Data as of December 20, 2020; error bars are the 90% confidence interval (CI).

Key Safety Outcomes

- In all patients, the most common AEs were skin hyperpigmentation (51.4%) and nausea (48.6%; Table 2)
- One participant had serious AEs of acute myocardial infarction and gastrointestinal hemorrhage that were considered unrelated to setmelanotide

Table 2. Treatment-Emergent AEs in Participants Receiving Setmelanotide

	Participants, n (%)
Treatment-emergent AEs occurring in ≥15% of participants	
Hyperpigmentation	19 (51.4)
Nausea	18 (48.6)
Injection site pruritus	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)
Serious AEs	1 (2.7)
Serious treatment-emergent AEs	0 (0)
Treatment-emergent AEs leading to discontinuation	7 (18.9)
Treatment-emergent AEs leading to death	0 (0.0)

AE, adverse event.

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1. Farooqi et al. *Diabetes*. 2006;55:2549-2553.
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