# Efficacy and Safety of Setmelanotide in Individuals With Obesity Due to POMC or LEPR Deficiency: Phase 3 Results From Pivotal and Supplemental Cohorts

**Sadaf Farooqi,[1] Jennifer Lynne Miller,[2] Olga Ohayon,[3] Guojun Yuan,[3] Cecilia Scimia,[3] Murray Stewart,[3] Jack Yanovski[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]National Institutes of Health, Bethesda, MD, USA

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Presenting Author:
Jennifer Lynne Miller
millejl@peds.ufl.edu

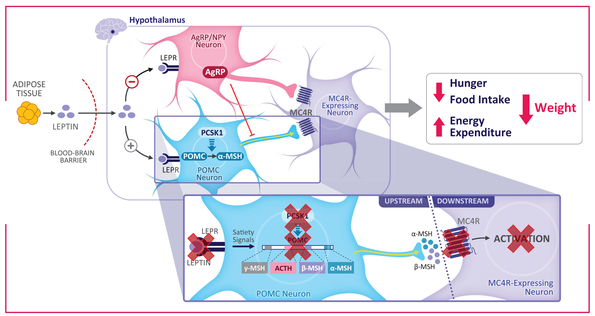
## Summary

- In the expanded data set from two Phase 3 clinical trials, setmelanotide was associated with weight loss and reductions in hunger in individuals with proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency and obesity
  - Setmelanotide demonstrated efficacy in POMC deficiency and, although some participants with LEPR deficiency did not lose ≥10% of baseline weight, substantial effects were observed in approximately half of those with LEPR deficiency
- No new safety concerns were reported, and setmelanotide was generally well tolerated in individuals with POMC or LEPR deficiency and obesity
- These additional data continue to support the earlier finding from the primary pivotal analysis that setmelanotide is beneficial in patients with POMC or LEPR deficiency and obesity

## Introduction

- The melanocortin-4 receptor (MC4R) pathway is critical in regulating appetite, body weight, and energy expenditure, and loss-of-function variants in this pathway can cause rare genetic disorders of obesity[1-3]
- Impaired signaling of the MC4R pathway by genetic variants in *POMC/PCSK1* or *LEPR* can lead to hyperphagia and early-onset, severe obesity (Figure 1)[1]

**Figure 1.** The MC4R pathway.[1-3]




ACTH, adrenocorticotropic hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

- In the primary analyses of two pivotal Phase 3 trials, the MC4R agonist setmelanotide was associated with significant reductions in body weight and hunger in 21 patients with obesity due to POMC or LEPR deficiency[1]

## Objective

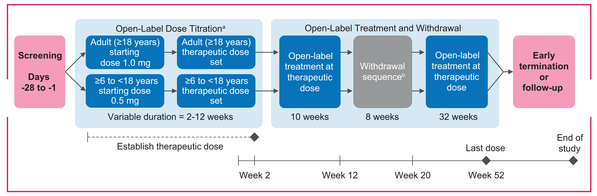
- To determine the effect of the MC4R agonist setmelanotide on body weight, hunger, and safety outcomes in an expanded cohort of patients with POMC/proprotein convertase subtilisin/kexin type 1 or LEPR deficiency and obesity from the pivotal Phase 3 clinical trials

## Methods

### Study Design

- In 2 single-arm, multicenter, Phase 3 trials of setmelanotide in patients with obesity due to POMC (NCT02896192) or LEPR deficiency (NCT03287960), patients aged ≥6 years received setmelanotide at the individualized therapeutic dose for 12 weeks
  - The first ~10 participants with POMC or LEPR deficiency were enrolled in each trial (pivotal cohort)
  - Because of the rarity of these genetic diseases, enrollment was kept open after pivotal participants were enrolled to collect additional supporting data from a supplementary cohort
- Patients with ≥5 kg weight loss (or ≥5% if weighing <100 kg at baseline) after 12 weeks of treatment with setmelanotide at the therapeutic dose entered an 8-week placebo-controlled withdrawal sequence, followed by an additional 32 weeks of open-label setmelanotide treatment (Figure 2)
  - This updated analysis includes patients enrolled in both the pivotal and supplemental cohorts

**Figure 2.** Study Design.




[a]The duration of the dose titration phase varied from 2 weeks to 12 weeks, with the final 2 weeks being at the therapeutic dose. [b]During the 8-week withdrawal sequence, patients received 4 weeks of treatment and 4 weeks of placebo in a blinded fashion.

### Key Entry Criteria

- All participants had biallelic loss-of-function variants in *POMC*/*PCSK1* or *LEPR* (homozygote or compound heterozygote); adults (aged ≥18 years) had a body mass index ≥30 kg/m$^2$; children or adolescents (aged ≥6 years to <18 years) had a weight >95th percentile for age
- Participants were excluded if they had recent diet and/or exercise regimens resulting in weight loss or stabilization or had prior gastric bypass surgery resulting in >10% weight loss with no evidence of weight regain

### Key Endpoints and Assessments

- Primary endpoint
  - Proportion of patients with ≥10% weight loss at ~52 weeks on setmelanotide
- Secondary endpoints
  - Mean percent change in body weight at ~52 weeks on setmelanotide
  - Mean percent change in "most" hunger score at ~52 weeks on setmelanotide in participants ≥12 years of age
  - Proportion of participants who achieved ≥25% reduction in "most" hunger score at ~52 weeks on setmelanotide
- Safety and tolerability of setmelanotide were assessed by reporting adverse events (AEs) in all participants who received ≥1 dose of setmelanotide

## Results

### Baseline Characteristics

- A total of 15 patients with POMC deficiency (10 pivotal cohort, 5 supplemental cohort) and 15 with LEPR deficiency (11 pivotal cohort, 4 supplemental cohort) were enrolled (Table 1)

**Table 1.** Baseline Characteristics

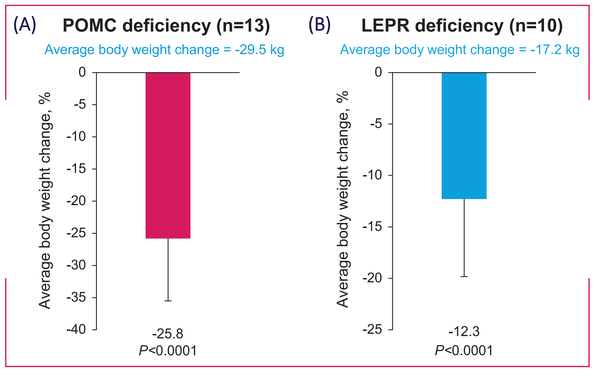
| | Patients, n (%) | |
|---|---|---|
| | POMC deficiency (N=15) | LEPR deficiency (N=15) |
| Age, mean (SD) [range], y | 17.2 (7.02) [7.0–30.0] | 21.7 (8.52) [8.0–37.0] |
| Male:Female, n (%) | 9 (60):6 (40) | 6 (40):9 (60) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 2 (13.3) | — |
| Not Hispanic or Latino | 11 (73.3) | 13 (86.7) |
| Unknown | 2 (13.3) | 2 (13.3) |
| Weight, mean (SD) [range], kg | 111.3 (35.8) [55.7–186.7] | 132.5 (39.3) [44.6–208.7] |
| BMI, mean (SD) [range], kg/m$^2$ | 39.2 (8.2) [26.6–53.3] | 49.2 (13.0) [28.1–69.7] |
| Most hunger score, mean (SD) [range][a] | 8.1 (0.8) [7.0–9.0][b] | 6.9 (1.1) [5.0–9.0][c] |

[a]Most hunger score was determined on a Likert scale ranging from 0 to 10 using the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" [b]n=7. [c]n=10. BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

### Efficacy

- A total of 85.7% of patients in the POMC trial (12/14; *P*<0.0001) and 53.3% of patients in the LEPR trial (8/15; *P*<0.0001) achieved ≥10% weight loss at 52 weeks
- The mean (standard deviation [SD]) percent change in body weight from baseline to 52 weeks was −25.8% (9.7%; *P*<0.0001) and −12.3% (7.5%; *P*<0.0001) in the POMC and LEPR trials, respectively (Figure 3)

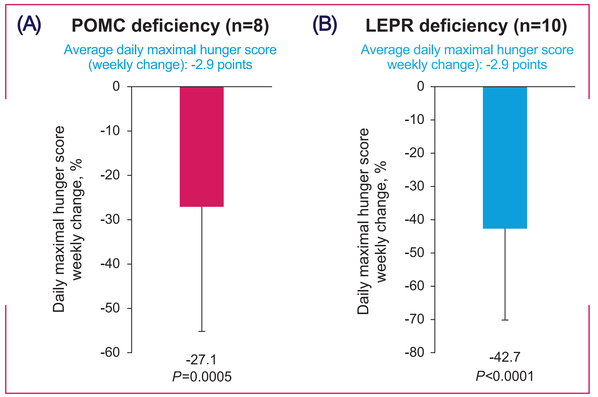
**Figure 3.** Average percent change in body weight in participants with **(A)** POMC and **(B)** LEPR deficiency obesity from baseline to ~52 weeks on therapeutic dose of setmelanotide.




Error bars are the standard deviation. LEPR, leptin receptor; POMC, proopiomelanocortin.

- In patients aged ≥12 years, the mean (SD) percent change in most hunger score at 52 weeks was −27.1% (−28.1%) and −42.7% (−27.5%) in the POMC and LEPR trials, respectively (Figure 4)

**Figure 4.** Average percent change in daily maximal hunger score in participants with **(A)** POMC and **(B)** LEPR deficiency obesity from baseline to ~52 weeks on therapeutic dose of setmelanotide.




Error bars are the standard deviation. LEPR, leptin receptor; POMC, proopiomelanocortin.

### Safety Outcomes

- There were no treatment-related serious AEs
- The most common AEs were injection site reaction and hyperpigmentation (Table 2)

**Table 2.** Treatment-Emergent AEs in Participants Receiving Setmelanotide

| | Patients, n (%) | |
|---|---|---|
| | POMC deficiency (N=15) | LEPR deficiency (N=15) |
| Treatment-emergent AEs[a] | | |
| Hyperpigmentation | 15 (100.0) | 11 (73.3) |
| Injection site erythema | 12 (80.0) | 11 (73.3) |
| Injection site pruritus | 9 (60.0) | 8 (53.3) |
| Injection site edema | 9 (60.0) | 6 (40.0) |
| Nausea | 8 (53.3) | 8 (53.3) |
| Headache | 8 (53.3) | 5 (33.3) |
| Vomiting | 8 (53.3)) | 2 (13.3) |
| Serious treatment-emergent AEs[b] | 6 (40.0) | 3 (20.0) |
| Treatment-emergent AEs leading to discontinuation | 0 (0.0) | 1 (6.7) |
| Treatment-emergent AEs leading to death | 0 (0.0) | 1 (6.7) |

[a]Treatment-emergent AEs reported in ≥50% of participants in either study. [b]There were no treatment-related serious AEs. AE, adverse event; LEPR, leptin receptor; POMC, proopiomelanocortin.

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**References: 1.** Clément et al. *Lancet Diabetes Endocrinol.* 2020;8:960-970. **2.** Yazdi et al. *PeerJ.* 2015;3:e856. **3.** Farooqi, O'Rahilly. *Nat Clin Pract Endocrinol Metab.* 2008;4:569-577.