Long-term Efficacy With Setmelanotide in Pediatric Patients With Acquired Hypothalamic Obesity

Ashley H. Shoemaker, MD[1]; Christian L. Roth, MD[2]; Susan A. Phillips, MD[3]; Jennifer L. Miller, MD[4]; Guojun Yuan, MD, PhD[5]; Cecilia Scimia, MD, PhD[5]; M. Jennifer Abuzzahab, MD[6]

[1]Vanderbilt University Medical Center, Nashville, TN, USA; [2]Seattle Children's Hospital, University of Washington, Seattle, WA, USA; [3]Pediatric Endocrinology, Rady Children's Hospital/University of California San Diego, San Diego, CA, USA; [4]Pediatric Endocrinology, Department of Pediatrics, College of Medicine, University of Florida, Gainesville, FL, USA; [5]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [6]Children's Minnesota, St. Paul, MN, USA

Poster #6

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Introduction

- Melanocortin-4 receptor (MC4R) pathway signaling in the hypothalamus plays a critical role in the regulation of energy balance[1]
- Hypothalamic injury due to brain tumors or surgical resection of those tumors, traumatic brain injury, inflammatory disease, or stroke can lead to acquired hypothalamic obesity (aHO) through potential MC4R pathway signaling impairment[2-4]
  - Disrupted MC4R signaling may cause hyperphagia (insatiable hunger accompanied by abnormal food-seeking behaviors) and accelerated and sustained weight gain[3-4]
- Treatment with the MC4R agonist setmelanotide resulted in consistent, clinically meaningful reductions across weight-related measures and hunger at Week 16 (primary time point) in a Phase 2, open-label aHO trial[5]

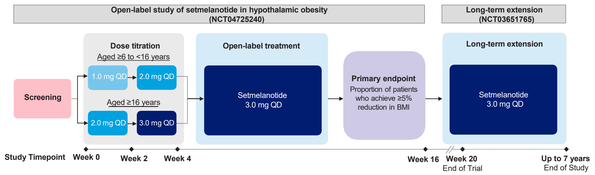
Objectives

- To assess the continued efficacy and safety after 2.5 years of setmelanotide treatment in pediatric participants (≥6 to <18 years), who comprised most of the Phase 2 trial population

Methods

- Participants who completed the 16-week Phase 2 index trial (NCT04725240), experienced a ≥5% reduction in body mass index (BMI) or had an investigator-determined clinically meaningful benefit, and exhibited adequate safety after 16 weeks of treatment were eligible to enroll in a long-term extension trial (LTE; NCT03651765; Figure 1)
  - Setmelanotide was administered in an age-dependent manner:
    - Participants ≥6 to <16 years initiated setmelanotide at 1.0 mg subcutaneous once a day (QD) for 2 weeks, followed by 2.0 mg QD for 2 weeks, and then 3.0 mg thereafter
    - Patients aged ≥16 years initiated setmelanotide at 2.0 mg QD for 2 weeks and escalated to 3.0 mg once a day
    - Following dose titration, all patients received setmelanotide 3.0 mg QD, as tolerated
    - During the LTE, setmelanotide treatment was continued at the dose established during the index trial
- The primary endpoint of the index trial was the proportion of participants who had a reduction in BMI of at least 5% from baseline after 16 weeks of setmelanotide treatment, compared with a historic control rate of less than 5% for patients with hypothalamic obesity
- The current analysis assessed changes from baseline in BMI, BMI Z score, percent of the BMI 95th percentile (%BMI95), and adverse events (AEs) in pediatric participants with aHO after 2.5 years of setmelanotide treatment

Figure 1. Study Design



BMI, body mass index; QD, once daily.

Results

- Of 13 pediatric participants who enrolled in the index trial, 12 participants entered the LTE
  - The mean age at index trial baseline was 11.9 years, 9 participants (75.0%) were male, most were white (83.3%), and craniopharyngioma was the most common tumor/damage type (83.3%; Table 1)
- At baseline, the mean BMI was 35.9 kg/m^2
- Ten participants completed 2.5 years of setmelanotide treatment

Table 1. Demographics and Baseline Characteristics

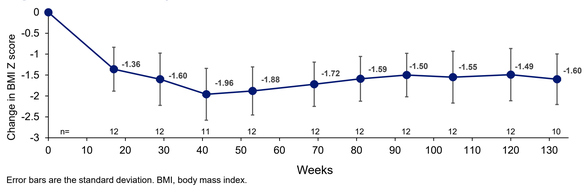
	Setmelanotide (n=12)
Age, mean±SD (range), y	11.9±3.0 (6.0–16.0)
Sex, n (%)	
Female	3 (25.5)
Male	9 (75.0)
Race, n (%)	
White	10 (83.3)
Black or African American	1 (8.3)
Native Hawaiian or Other Pacific Islander	1 (8.3)
Ethnicity, n (%)	
Hispanic or Latino	4 (33.3)
Not Hispanic or Latino	8 (66.7)
Tumor/damage type, n (%)	
Craniopharyngioma	10 (83.3)
Hypothalamic hamartoma	2 (16.7)
Weight, mean (SD), kg	94.1 (31.5)
BMI, mean (SD), kg/m^2	35.9 (6.5)
BMI Z score, mean (SD)*	3.98 (0.94)
Percentage of the 95th percentile of BMI, mean (SD)†	145.8 (21.9)
Waist circumference, mean (SD), cm	108.8 (16.7)

*BMI Z score calculated according to the World Health Organization 2007 method.
†Percentage of the 95th percentile of BMI calculated according to the Centers for Disease Control and Prevention 2022 method.
%BMI95, percent of the 95th percentile; BMI, body mass index; SD, standard deviation.

Efficacy

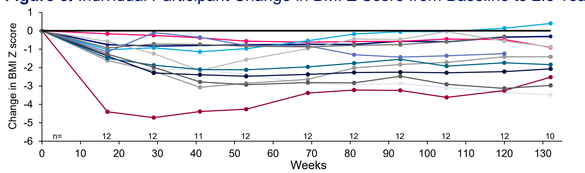
- The mean (SD) change from baseline in BMI Z score was −1.60 (1.21) at 2.5 years (Figure 2; individual participant data in Figure 3)

Figure 2. Mean Change in BMI Z Score from Baseline to 2.5 Years



Error bars are the standard deviation. BMI, body mass index.

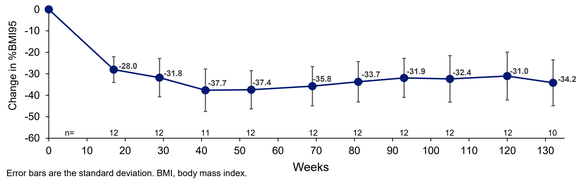
Figure 3. Individual Participant Change in BMI Z Score from Baseline to 2.5 Years



A clinically meaningful reduction is generally considered a ≥0.2 reduction in BMI Z-score. Two patients did not have BMI Z-score data available at the 2.5 year timepoint. BMI, body mass index.

- The mean (SD) change in %BMI95 was −34.2 (21.4) percentage points at 2.5 years (Figure 4)

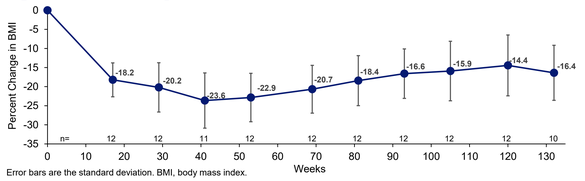
Figure 4. Mean Change in %BMI95 from Baseline to 2.5 Years



Error bars are the standard deviation. BMI, body mass index.

- After 2.5 years, the mean (SD) change from baseline in BMI was −16.4% (14.4; Figure 5)

Figure 5. Mean Change in Percent BMI from Baseline to 2.5 Years



Error bars are the standard deviation. BMI, body mass index.

Safety

- The most common AEs were skin hyperpigmentation (58.3%), nausea (50.0%), upper respiratory tract infection (50.0%), headache (41.7%), and vomiting (41.7%; Table 2)

Table 2. Safety

n (%)	Setmelanotide (n=12)
AEs	12 (100.0)
AE leading to treatment or study discontinuation	0
Serious AEs	4 (33.3)
AE resulting in death on study	0
AE in ≥20% of participants	
Skin hyperpigmentation	7 (58.3)
Nausea	6 (50.0)
Upper respiratory tract infection	6 (50.0)
Headache	5 (41.7)
Vomiting	5 (41.7)
Erection increased	4 (33.3)
Injection site induration	4 (33.3)
Abdominal pain	3 (25.0)
Back pain	3 (25.0)
COVID-19	3 (25.0)
Injection site pain	3 (25.0)
Treatment-related AEs	11 (91.7)
Treatment-related serious AEs	0

AE, adverse event; COVID-19, coronavirus disease 2019.

Conclusions

- Two and a half years of setmelanotide treatment was associated with robust and sustained reductions across age-related weight measures in pediatric patients with aHO
- These data demonstrate the long-term efficacy and safety of setmelanotide in patients with aHO

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