Trial Design of a Double-blind, Randomized, Placebo-Controlled, Phase 3 Study of Setmelanotide in Patients With Hypothalamic Obesity

FRI-065

Christian L. Roth, MD[1,2]; Ashley H. Shoemaker, MD, MSCI[3]; Michael Gottschalk, MD, PHD[4]; Jennifer L. Miller, MD[5]; Guojun Yuan, PhD[6]; Sonali Malhotra, MD[6,8]; Cecilia Scimia, MD, PhD[6]; Shana McCormack, MD[9,10]; M. Jennifer Abuzzahab, MD[11]; on behalf of the TRANSCEND Trial Group

[1]Seattle Children's Research Institute, Seattle, WA, USA; [2]Division of Endocrinology, Department of Pediatrics, University of Washington, Seattle, WA, USA; [3]Ian Burr Division of Endocrinology and Diabetes, Vanderbilt University Medical Center, Nashville, TN, USA; [4]Pediatric Endocrinology, University of California San Diego/Rady Children's Hospital, San Diego, CA, USA; [5]Pediatric Endocrinology, Department of Pediatrics, University of Florida College of Medicine, Gainesville, FL, USA; [6]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Harvard Medical School, Boston, MA, USA; [9]Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [10]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [11]Pediatric Endocrinology and Diabetes, Children's Minnesota, Saint Paul, MN, USA

Presenting Author:
Ashley H. Shoemaker
ashley.h.shoemaker@vumc.org

Introduction

- Hypothalamic obesity is an acquired form of rapid-onset, severe obesity that occurs most frequently after hypothalamic damage resulting from surgical resection or radiation of brain tumors[1-3]
- Injury to the hypothalamic region can impair signaling of the melanocortin-4 receptor (MC4R) pathway, a critical regulator of satiety and energy balance[1,2]
  - Disruption of the MC4R pathway is associated with pathologic, insatiable hunger (ie, hyperphagia) and severe obesity[4,5]
- Hypothalamic obesity is associated with reduced energy expenditure along with multiple pituitary hormone deficiencies, including hypothyroidism, adrenocorticotropic hormone deficiency, growth hormone deficiency, and diabetes insipidus[3]
- Weight gain and hyperphagia observed in hypothalamic obesity are often refractory to traditional weight management strategies[1-5]
- In a Phase 2 trial, the selective MC4R agonist setmelanotide demonstrated reduction in weight and hunger among a heterogeneous population of patients with hypothalamic obesity who had varied tumor presentation and age[6]
  - Overall, 88.9% of patients (16 of 18) achieved the primary endpoint of ≥5% reduction in body mass index (BMI) after 16 weeks of open-label setmelanotide treatment
  - Maximal daily hunger score was reduced by 45.0%
  - All patients adherent to treatment, including those who discontinued study drug, lost weight after 16 weeks of treatment (mean change in BMI, −15.4%; n=17)

Objective

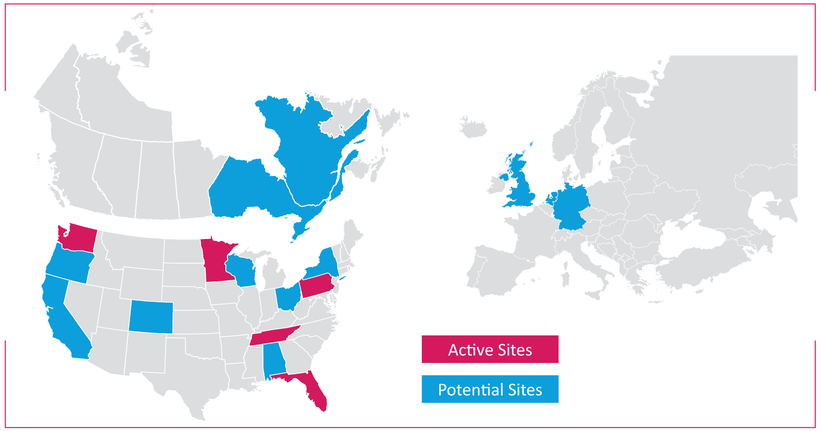
- To describe the study design of a Phase 3 trial assessing the efficacy and safety of setmelanotide in patients with acquired hypothalamic obesity (NCT05774756)

Methods

Patients and eligibility criteria[7]

- Approximately 120 patients will be enrolled across up to 35 sites globally
  - Active sites as of May 2023 are University of Florida (Gainesville, FL, USA); Children's Minnesota (Saint Paul, MN, USA); Vanderbilt University School of Medicine (Nashville, TN, USA); Children's Hospital of Philadelphia (Philadelphia, PA, USA); and Seattle Children's Hospital, Research and Foundation – Center for Integrative Brain Research (Seattle, WA, USA; Figure 1)

Figure 1. Active and potential site locations Q1, 2023.[7,*]



*Maps not to relative scale.

- Eligible patients ≥4 years of age with documented evidence of acquired hypothalamic obesity will be enrolled (Table 1)

Table 1. Key Eligibility Criteria

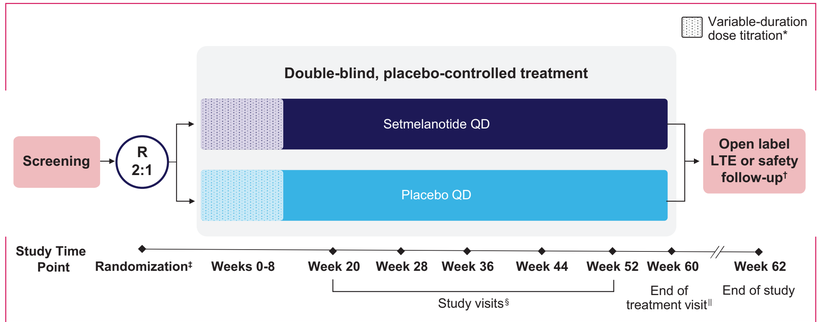
Key inclusion criteria	Key exclusion criteria
■ ≥4 years of age	■ Diagnosis of PWS or ROHHADNET
■ Documented evidence of acquired hypothalamic obesity, defined as	■ Obesity due to genetic or syndromic conditions before hypothalamic injury
• Diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region with treatment (ie, surgery, chemotherapy, radiation) received ≥6 months before screening, or	■ Weight loss in the prior 3 months
• Documented injury to the hypothalamus ≥6 months before screening for which surgery or radiation is not indicated	• >2% body weight for those aged ≥18 years
■ Documented weight gain associated with hypothalamic injury (before or following therapy), and	• >2% BMI reduction for those aged <18 years
• BMI ≥30 kg/m^2 for those aged ≥18 years	■ Bariatric surgery or procedure within the last 2 years
• BMI ≥95th percentile for age and sex for those aged <18 years	■ HbA_{1c} >11.0%
	■ GFR <30 mL/min/1.73 m^2
	■ Significant dermatologic findings relating to melanoma, or a history or close family history of skin cancer or melanoma
	■ Severe psychiatric disorder or major depressive disorder

BMI, body mass index; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; PWS, Prader-Willi syndrome; ROHHADNET, rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome.

Study design[7]

- Enrolled patients will be randomized 2:1 and stratified by age to receive setmelanotide or placebo
  - Setmelanotide or placebo equivalent will be administered initially at 0.5 mg once daily, and thereafter escalated in 0.5- and 1.0-mg increments to an individual therapeutic dose based on age and weight
  - For patients <6 years of age, the dose will be titrated to a maximum of 1.5 mg for those with weight <20 kg, 2.0 mg for those with weight 20 to <25 kg, 2.5 mg for those with weight 25 to <30 kg, or 3.0 mg for those with weight ≥30 kg
  - For patients ≥6 years of age and with weight ≥30 kg, the dose will be titrated to a maximum of 3.0 mg
- Following randomization, patients will receive double-blinded treatment for up to 60 weeks (Figure 2)
  - Upon trial completion, patients may be eligible to enter an open-label long-term extension trial of setmelanotide

Figure 2. Study design.



*The initial dose of 0.5 mg to be escalated in increments of 0.5 to 1.0 mg until the patient reaches an individual therapeutic regimen based on age and weight. †Patients completing the trial may be eligible to participate in an open-label LTE trial; the safety follow-up visit is required only for patients prematurely discontinuing treatment or those completing the trial who do not enroll in the LTE. ‡Baseline is defined as the last available measurement before randomization. §Visits completed in clinic, at home, or via telehealth. ‖In-clinic visit.
LTE, long-term extension; QD, once daily; R, randomization.

Endpoints and analysis[7]

- The primary endpoint is the mean percent change in BMI after 52 weeks of treatment with setmelanotide versus placebo
- Secondary endpoints, including additional weight parameters, hunger, hyperphagia symptoms, and quality of life, are shown in Table 2
- Exploratory endpoints include change after 52 weeks in physical activity (measured by actigraphy), fatigue (via Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]/Peds FACIT-F scale), Impacts of Hyperphagia score, caregiver health status (via EuroQol-5 Dimension scale), key biomarkers (eg, leptin), and body composition
- Safety and tolerability will be assessed by the frequency and severity of adverse events, as well as changes in ambulatory blood pressure and heart rate

Table 2. Trial Endpoints After 52 Weeks of Setmelanotide Versus Placebo

Primary endpoint

- Mean percent change in BMI

Key secondary endpoints

- The composite proportion of patients with ≥5% reduction in BMI (≥18 years of age) and BMI Z score reduction of ≥0.2 points in pediatric patients (<18 years of age)
- The proportion of all patients with ≥5% reduction in BMI
- Mean change in the weekly average of the daily most hunger score in those aged ≥12 years

Additional secondary endpoints

- Proportion of patients with ≥2-point reduction in weekly average of daily most hunger score
- Mean change in Symptoms of Hyperphagia total score
- Proportion of patients achieving ≥10% BMI reduction
- Proportion of patients achieving ≥10% weight reduction
- Mean percent change in weight in those aged ≥18 years
- Mean BMI Z score and BMI percentile reduction in those aged <18 years
- Proportion of patients with ≥0.2-point BMI Z score reduction in those aged <18 years
- Proportion of patients with BMI <30 kg/m^2 in those aged ≥18 years or <95th BMI percentile in those aged <18 years at the end of the intervention
- Mean change in IWQOL-Lite in those aged ≥18 years and IWQOL-Kids in those aged <18 years (physical functioning score and total score for both)
- Change in waist circumference in those aged ≥18 years
- Change in cardiometabolic parameters

BMI, body mass index; IWQOL, Impact of Weight on Quality of Life.

Conclusions

- There are no currently approved treatments for hypothalamic obesity, and most patients do not respond to traditional weight management strategies; thus, novel treatments are needed
- This randomized, double-blind, placebo-controlled, Phase 3 trial will explore the efficacy and safety of setmelanotide for the potential treatment of acquired hypothalamic obesity
- Results from this study will build upon those from a Phase 2 trial that demonstrated significant reductions in weight and hunger with setmelanotide treatment in this population[6]

Acknowledgments: This study is sponsored by Rhythm Pharmaceuticals, Inc. Medical writing and editorial assistance was provided under the direction of the authors by MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

Disclosures: MJA has received compensation for consulting, advisory board participation, and speaking engagements from Rhythm Pharmaceuticals, Inc.; Pfizer; Endo Pharmaceuticals; and ConSynance Therapeutics. MJA's institution has received research support from Rhythm Pharmaceuticals, Inc.; Ascendis Pharma; Novo Nordisk; Levo Therapeutics; Lumos Pharma; Saniona; and Soleno Therapeutics. AHS has received payments from Rhythm Pharmaceuticals, Inc., and Saniona for advisory boards and lectures. AHS's institution has received research support from Rhythm Pharmaceuticals, Inc. MG has received compensation for consulting and participation on advisory boards from Rhythm Pharmaceuticals, Inc. MG's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. JM has received study funding from Rhythm Pharmaceuticals, Inc. GY is an employee of Rhythm Pharmaceuticals, Inc., and has company-awarded RSU and options. SM is an employee and stockholder in Rhythm Pharmaceuticals, Inc. CS is an employee of Rhythm Pharmaceuticals, Inc., and has company-awarded RSU and options. CLR's institution has received research support from Rhythm Pharmaceuticals, Inc.

References: 1. Abuzzahab et al. *Horm Res Paediatr.* 2019;91:128-136. **2.** Erfurth. *Neuroendocrinology.* 2020;110:767-779. **3.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **4.** Yazdi et al. *PeerJ.* 2015;3:e856. **5.** van Iersel et al. *Endocr Rev.* 2019;40:193-235. **6.** Roth et al. Presented at: ObesityWeek; November 1-4, 2022; San Diego, CA. **7.** ClinicalTrials.gov. NCT05774756. https://clinicaltrials.gov/ct2/show/NCT05774756. Updated June 1, 2023. Accessed June 9, 2023.