RESTORE: Real-world Study of Setmelanotide in Patients With MC4R Pathway Diseases

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Summary

- SeTmelanotide fOr Hyperphagia and ChRonic Weight ManagEment (RESTORE) is a multicountry, prospective, observational, longitudinal study to assess the real-world effectiveness of setmelanotide among patients with Bardet-Biedl syndrome (BBS) and proopiomelanocortin (POMC; including variants in *PCSK1*) or leptin receptor (LEPR) deficiency and their caregivers
- Data from RESTORE will provide further evidence on hyperphagia-related symptoms and behaviors, as well as the impact of setmelanotide on health-related quality of life (HRQOL) in patients and their caregivers

Introduction

- Setmelanotide has demonstrated efficacy in clinical trials of patients with hyperphagia (pathologic, insatiable hunger) and obesity due to rare melanocortin-4 receptor (MC4R) pathway diseases, including BBS and POMC (including biallelic variants in *PCSK1*) or LEPR deficiency and is approved by the United States Food and Drug Administration and Health Canada for use in these patient populations[1-4]
- While the safety and efficacy of setmelanotide have been established in clinical trials, real-world evidence is needed to understand the utility of the treatment in clinical practice; particularly for rare diseases, including those due to MC4R pathway deficiencies, understanding patient and caregiver experiences with a new treatment have become increasingly important[5-7]

Objectives

- To assess hyperphagia, its impact, and HRQOL in patients with BBS, POMC deficiency (including biallelic variants in *PCSK1*), or LEPR deficiency prescribed setmelanotide in clinical settings in the United States and Canada
- To assess sleep activity and patterns in these patient populations

Methods

Participants and eligibility criteria

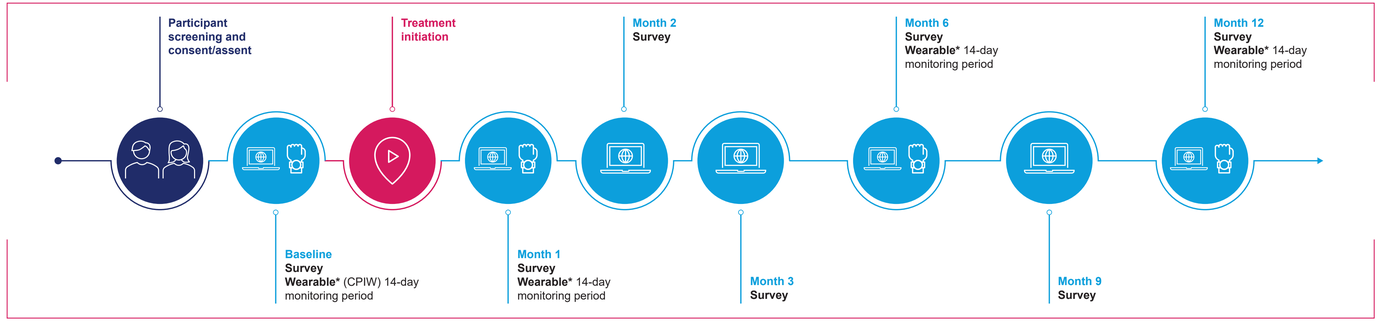
- Patients aged ≥6 years and caregivers aged ≥18 years in the United States and Canada who are able to respond to a survey in English and are currently consented into the Rhythm InTune Patient Support Program are eligible for the study (Table 1)
  - The InTune Patient Support Program provides support to patients treated with setmelanotide and their caregivers by sharing resources, education, and information tailored to fit their unique needs
  - Interested patients or caregivers from InTune will complete a screener, and those who meet the criteria will be given the option to provide consent or assent into the study

Table 1. Eligibility Criteria

Patients	Caregivers
• Aged ≥6 years at the time of enrollment • Able to read English • Have not been previously treated with setmelanotide • Not currently enrolled in any clinical trials • Prescribed setmelanotide, but not yet initiated treatment for BBS, POMC,* or LEPR deficiency • To begin setmelanotide treatment within 10 weeks of study enrollment	• Aged ≥18 years • Able to read English • Confirmed legal guardian of a patient with BBS and POMC* or LEPR deficiency who meets the eligibility criteria • Have cared for the patient with BBS, POMC,* or LEPR deficiency for ≥6 months • Not a paid professional caregiver

*Including variants in *PCSK1*. BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; POMC, proopiomelanocortin.

Figure. Study design.



*A subset of patient participants will be invited to receive a wearable device to assess activity levels and sleep patterns. CPIW, CentrePoint® Insight Watch.

Study design

- Participants will complete secure online surveys at baseline (ie, before treatment) and at 6 posttreatment initiation time points over a 1-year period (Figure)
  - Patient participants will be sequentially invited, until reaching a target sample size for the substudy, to receive a wearable device (CentrePoint® Insight Watch; CPIW) to assess activity levels and sleep patterns during the 1-year period
- Patient and caregiver surveys will include multiple patient-reported outcomes (PROs) and observer-reported outcomes (obsROs; Table 2)

Analysis of study outcomes

Summary of baseline characteristics

- Descriptive analyses will be conducted to summarize the characteristics of participants
- Baseline summary statistics for treatment use and disease-related outcome variables (eg, treatment satisfaction, hyperphagia-related signs and symptoms, disease impact, and HRQOL) will be included
- Continuous variables will be summarized with the mean, median, and standard deviation; categorical variables will be summarized with the frequency, count, and percentage

PRO and ObsRO scoring

- Total and domain scores for established assessments (Table 2) will be calculated on the basis of the assessment scoring manual and summarized descriptively using the mean, median, and standard deviation

Table 2. Study Outcomes and Assessments for PROs and ObsROs

Patients	Caregivers
Outcomes	
• Hyperphagia symptoms • Medical history • Treatment adherence • Weight management programs and treatment • Comorbidities/Complications and comedications • Disease impact on psychological well-being and HRQOL, treatment satisfaction, work/school/activity status, and patient global assessment	• Psychological well-being • Treatment satisfaction • Impact on activities of daily living, work status, and family dynamics
Patients	**Caregivers**
Assessments	
• Symptoms of Hyperphagia Questionnaire: Patient Version[9] • Impacts of Hyperphagia Questionnaire: Patient Version[8] • PROMIS v1.2 Global Health in adults* • PROMIS pediatric short form – cognitive function 7a – v1.0 in patients aged 12-17 years* • WPAI or WPAI+CIQ	• Symptoms of Hyperphagia Questionnaire: Caregiver Version[6] • Impacts of Hyperphagia Questionnaire: Caregiver Version[7] • IWQOL-Lite*, IWQOL-Kids*, or IWQOL-Kids Parent Proxy† • PROMIS v1.2 Global Health • PROMIS Parent Proxy Scale v1.0‡ • PROMIS parent proxy short form – cognitive function 7a – v1.0‡ • WPAI • RIOFS

*Administered to patients who can self-report. †Administered to caregivers of patients aged 12-17 years who cannot self-report or are aged <12 years. ‡Administered to caregivers of patients who cannot self-report. HRQOL, health-related quality of life; IWQOL, Impact of Weight on Quality of Life; ObsRO, observer-reported outcome; PRO, patient-reported outcome; PROMIS, Patient Reported Outcome Measurement Information System; RIOFS, Revised Impact on Family Scale; WPAI, Productivity and Activity Impairment; WPAI+CIQ, WPAI plus Classroom Impairment Questions.

Analysis of setmelanotide use and real-world outcomes

- Setmelanotide use and disease-related outcomes among patients (eg, hyperphagia symptoms, disease impact and HRQOL, comorbidities and/or complications, setmelanotide satisfaction, work and school activities) will be described and compared with baseline values
  - Unadjusted statistical comparisons between the posttreatment outcomes and baseline values will be conducted using unpaired *t* tests for continuous variables and chi square or Fisher's exact tests for categorical variables

CPIW substudy

- Activity levels and sleep patterns at baseline and at applicable follow-up periods will be described
  - Data from the follow-up periods will be compared with the baseline values
- Similar descriptive statistics for continuous variables will summarize the measurements captured by CPIW

Current Status

- RESTORE is the first real-world study of setmelanotide in the United States and Canada, has received institutional review board approval, and is actively enrolling
- This study will provide more supportive evidence for clinicians regarding the effectiveness of setmelanotide in real-world clinical practice

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