Design of a Phase 2, Double-Blind, Placebo-Controlled Trial of Setmelanotide in Patients With Genetic Variants in the Melanocortin-4 Receptor Pathway

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266

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Summary

- **The Phase 2 DAYBREAK trial will evaluate setmelanotide for weight loss and hunger reduction in individuals who have a variant in at least one of 31 genes associated with the melanocortin-4 receptor (MC4R) pathway**
- **Understanding the effect of setmelanotide in individuals with genetic variants within the MC4R pathway can expand access to those living with rare genetic diseases of obesity**
- **Enrollment of the first patient is expected by the end of 2021**

Introduction

- Rare genetic diseases of obesity are distinct from general obesity and are often driven by variants in the MC4R pathway, which regulates energy balance and body weight homeostasis[1,2]
  - Rare variants in key MC4R pathway genes, such as *LEPR*, *POMC*, and *PCSK1*, have been associated with obesity irrespective of environmental factors[1,2]
  - Other gene variants within the MC4R pathway, including *LEP*, *SIM1*, *MRAP2*, and *KSR2*, are also associated with obesity[3,4]
- Setmelanotide, a selective agonist of MC4R, is approved to treat obesity due to pathogenic variants, likely pathogenic variants, or variants of uncertain significance in *LEPR*, *POMC*, or *PCSK1*[5]
  - Treatment with setmelanotide in two Phase 3 trials resulted in ≥10% weight loss and significant hunger reduction in those with biallelic variants in *LEPR* or *POMC*[6]
- DAYBREAK is a Phase 2, 2-stage trial with an open-label run-in period followed by a double-blind, placebo-controlled period that will evaluate the effect of setmelanotide in patients with variants in an additional 31 MC4R pathway genes

Objective

- To evaluate the safety, efficacy, and effect of setmelanotide for reducing weight and hunger in patients with genetic variants in the MC4R pathway

Methods

Participants and Eligibility Criteria

- Stage 1 of the study will enroll ~500 eligible patients (**Table 1** and **Box 1**) with the intention to include ~130 of those patients in Stage 2
  - Sample size was determined by a power analysis to detect significance between the 2 groups (pooled treatment across genotype versus pooled placebo) with a 2-sided alpha level of 5% and an expected premature dropout rate of 5% in Stage 2

Table 1. Key Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
▪ Preidentified variant in the MC4R pathway	▪ Recent diet or exercise resulting in >3% weight loss
▪ Aged ≥6 to 65 years	▪ Bariatric surgery within 6 months of enrollment
▪ BMI ≥40 kg/m^2 (≥18 years old) or BMI ≥97th percentile (6 to ≤17 years old)	▪ Diagnosis or features of syndromic obesity
	▪ Glycated hemoglobin >10.0%
	▪ Glomerular filtration rate <60 mL/min

BMI, body mass index; MC4R, melanocortin-4 receptor.

Box 1. MC4R Pathway Genes Eligible For Enrollment[a]

CPE	*PLXNA2*
CREBBP	*PLXNA3*
DNMT3A	*PLXNA4*
HTR2C	*RPGRIP1L*
ISL1	*SEMA3A*
KSR2	*SEMA3B*
LEP	*SEMA3C*
MAGEL2	*SEMA3D*
MC3R	*SEMA3E*
MC4R	*SEMA3F*
MECP2	*SEMA3G*
MRAP2	*SIM1*
NRP1	*TBX3*
NRP2	*TRPC5*
PHIP	*TUB*
PLXNA1	

[a]Patients with variants categorized as pathogenic, likely pathogenic, or a variant of uncertain significance based on American College of Medical Genetics criteria. MC4R, melanocortin-4 receptor.

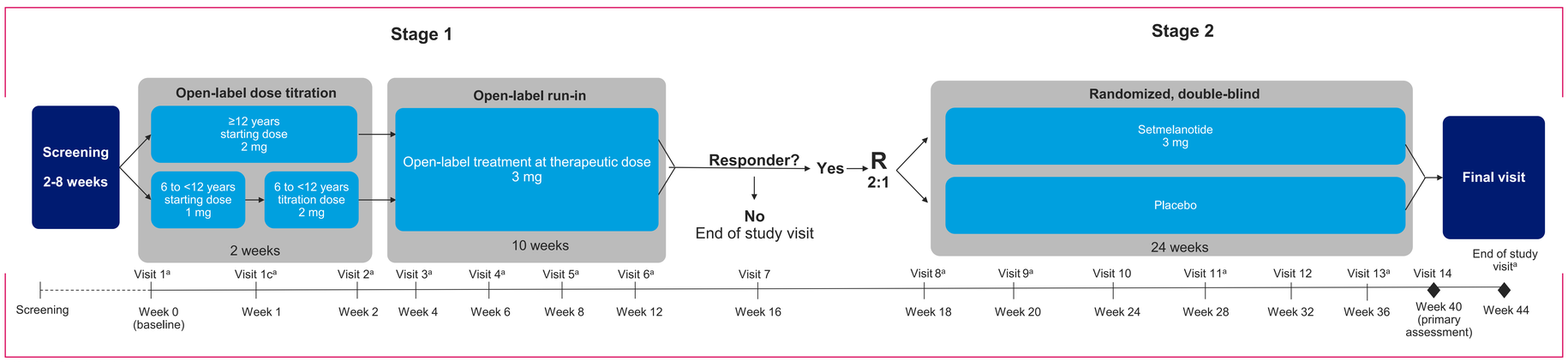
Study Design

- Stage 1 consists of 16 weeks of daily subcutaneous setmelanotide, which will be administered by patients or caregivers
  - Patients ≥12 years old will receive daily dosages of 2 mg for 14 days, followed by 3 mg thereafter; for patients aged 6 to <12 years, daily dosages will be 1 mg for 7 days, 2 mg for 7 days, and 3 mg thereafter (**Figure 1**)
- Stage 2 continues with the subcutaneous injections but is a 24-week, double-blind, randomized (2:1, setmelanotide:placebo) trial
  - Patients are eligible for Stage 2 if they achieve weight loss of ≥5% less than baseline weight (patients ≥18 years old) or a decrease in body mass index (BMI) Z score of ≥0.10 (patients <18 years old)
  - If a patient's weight increases by ≥5% from the Stage 2 entry weight, the patient is eligible for open-label rescue treatment with setmelanotide

Endpoints and Analysis

- Primary endpoint
  - Proportion of patients completing Stage 2 who are responders (achieve ≥10% weight loss or ≥0.3-point reduction from baseline in BMI Z score for those aged ≥18 years old or <18 years old, respectively) compared with placebo at Week 40
- Secondary endpoints
  - Proportion of enrolled patients who enter Stage 2 (ie, responders)
  - Mean and percent change in body weight from baseline (≥18 years old) or mean change in BMI Z score from baseline (<18 years old) compared with placebo
  - Mean percent change in waist circumference from baseline in patients ≥12 years old compared with placebo
  - Mean percent change in weekly average hunger score from baseline
  - Assessment of quality of life by EuroQol 5 Dimension 5 Level assessment and the Impact of Weight on Quality of Life-Lite
- Exploratory endpoints
  - Change from baseline in fasting glucose, glycated hemoglobin, and lipid profiles
  - Proportion of setmelanotide responders, mean change in body weight, and change in hunger score stratified by gene variant
- Safety will be assessed by frequency of adverse events, laboratory evaluations, and vital signs
- Analysis of the primary endpoint will be performed by Fisher's exact test with 95% confidence intervals reported

Figure 1. Study design for Stage 1 and Stage 2 of a Phase 2 trial of setmelanotide.



[a]Virtual visit. R, randomization.

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