Setmelanotide in Patients With Obesity Due to Heterozygous Variants in *POMC*, *LEPR*, *NCOA1*, or *SH2B1* Genes: Design of EMANATE—a Placebo-Controlled Phase 3 Trial

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* Potential conflict of interest may exist. Refer to the Meeting App.

RF24 | PSUN96

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Summary

- **EMANATE (NCT05093634) is a Phase 3, randomized, double-blind, placebo-controlled trial of setmelanotide in patients with obesity and *POMC*, *PCSK1*, *LEPR*, *NCOA1*, or *SH2B1* variants**
- **The trial will provide evidence for setmelanotide treatment for potential weight management in an expanded population of patients with rare genetic diseases of obesity**

Introduction

- Variants of genes in the melanocortin-4 receptor (MC4R) pathway, including variants in the leptin receptor gene (*LEPR*), proopiomelanocortin gene (*POMC*), proprotein convertase subtilisin/kexin type 1 gene (*PCSK1*), nuclear receptor coactivator 1 gene (*NCOA1*; also referred to as *SRC1*), and SH2B adaptor protein 1 gene (*SH2B1*), are associated with dysregulation of food intake and energy expenditure[1-3]
- In a Phase 2 trial, the MC4R agonist setmelanotide led to ≥5% reduction in body weight after 3 months in 34% of patients with heterozygous POMC, PCSK1, or LEPR insufficiency[4]; 30% with obesity due to SRC1 deficiency caused by a variant in *NCOA1*[5]; and 37% with SH2B1 deficiency (including chromosomal 16p11.2 deletion encompassing *SH2B1*)[6]
- EMANATE is a Phase 3, randomized, double-blind, placebo-controlled trial of setmelanotide in patients with obesity and *POMC*, *PCSK1*, *LEPR*, *NCOA1*, or *SH2B1* variants with 4 similar independent substudies based on genetic variant (NCT05093634)

Objective

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

Methods

Patient Population

- The trial will enroll ~400 eligible patients (Table and Box)

Table. Key Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
Preidentified genetic variant in the MC4R pathway	≥2% weight loss in the prior 3 months and/or recent bariatric surgery
Aged 6-65 years	Reported history of significant liver or kidney disease
Current obesity defined as • BMI ≥30 kg/m^2 in patients ≥18 years old • BMI ≥95th percentile in patients 6-17 years old	Significant psychiatric disorder(s) or suicidal ideation, attempt, or behavior
Reported history of • Childhood obesity • Hyperphagia • Lifestyle intervention of diet and exercise	Clinically significant pulmonary, cardiac, or oncologic disease and/or HbA_{1c} >10% at screening

BMI, body mass index; HbA_{1c}, glycated hemoglobin; MC4R, melanocortin-4 receptor.

Box. Gene Variants in MC4R Pathway Eligible for Enrollment

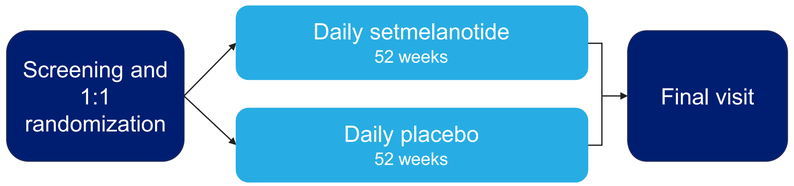
Substudy	Variant type	Included genes	ACMG classification
035a	Heterozygous	*POMC* *PCSK1*	Pathogenic, likely pathogenic, suspected pathogenic
035b	Heterozygous	*LEPR*	Pathogenic, likely pathogenic, suspected pathogenic
035c	Heterozygous, homozygous, or compound heterozygous	*NCOA1*	Pathogenic, likely pathogenic, VUS[a]
035d	Heterozygous, homozygous, or compound heterozygous	*SH2B1* Chromosomal 16p11.2 deletion encompassing *SH2B1*	Pathogenic, likely pathogenic, VUS

[a]No *NCOA1* variants are deemed pathogenic or likely pathogenic because of the gene being classified as a "gene of uncertain significance" clinically.
ACMG, American College of Medical Genetics; MC4R, melanocortin-4 receptor; VUS, variant of uncertain significance.

Trial Design

- Within each substudy, patients will be randomized 1:1 to receive daily subcutaneous injections of setmelanotide or placebo for 52 weeks (Figure)

Figure. Trial design for EMANATE, a Phase 3, randomized, double-blind, placebo-controlled trial.



Outcome Measures

- The primary outcome is the mean change in body weight, assessed as percent change in body mass index, in patients who receive setmelanotide compared with placebo
- Key secondary outcomes include additional measurements of effects on weight-related, hunger, and hyperphagia endpoints
- Safety will be assessed by frequency and severity of adverse events

Current Status

- The EMANATE trial is currently ongoing and enrolled the first patient in April 2022

Conclusions

- This placebo-controlled Phase 3 trial will generate evidence for setmelanotide treatment for potential improvements in weight- and hunger-related measures in an expanded population of patients with obesity and rare genetic variants in the leptin-melanocortin pathway

Acknowledgments:

This trial is sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided under the direction of the authors by Rachel Haake, PhD, and David Boffa, ELS, of MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc. Data in this poster were previously presented at Zoom Forward 22; May 4-7, 2022; Maastricht, The Netherlands.

References:

1. Yazdi et al. *PeerJ*. 2015;3:e856.
2. Yang et al. *Nat Commun*. 2019;10:1718.
3. Doche et al. *J Clin Invest*. 2012;122:4732-4736.
4. Farooqi et al. Poster presented at: Overcoming Obesity; September 23-26, 2021; Chicago, IL.
5. Farooqi et al. Poster presented at: ObesityWeek®; November 1-5, 2021; Virtual.
6. Argente et al. Poster presented at: ObesityWeek®; November 1-5, 2021; Virtual.