VENTURE: Design of a Phase 3 Multicenter, 1-Year, Open-Label Trial of Setmelanotide in Pediatric Patients Aged 2 to <6 Years With Rare Genetic Diseases of Obesity

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Summary

- **The 1-year, open-label, Phase 3 VENTURE trial (NCT04966741) will provide safety and efficacy data for the potential early treatment of patients aged 2 to <6 years with Bardet-Biedl syndrome (BBS) or obesity due to biallelic variants in *POMC*, *PCSK1*, or *LEPR***

Introduction

- Rare genetic diseases of obesity are often driven by gene variants in the melanocortin-4 receptor (MC4R) pathway[1]
- The MC4R agonist setmelanotide demonstrated significant reductions in body weight, body mass index, and hunger in patients aged ≥6 years old with various rare genetic diseases of obesity, including BBS or obesity caused by biallelic variants in *POMC*, *PCSK1*, or *LEPR*[2,3]
- While these rare genetic diseases of obesity are characterized by hyperphagia and severe obesity with an onset during the first years of life, few clinical trials have evaluated pharmacotherapies for patients aged <6 years with obesity[1,4]
- Because obesity in childhood is associated with increased mortality, early intervention represents an important unmet need while safe and efficacious therapeutic options for this population are limited[5,6]
- Additionally, early onset of severe hunger and subsequent obesity may be associated with learning difficulties.[7] Therefore, early recognition of these disorders and timely treatment initiation have the potential to substantially affect long-term outcomes

Objective

- The Phase 3 VENTURE trial (NCT04966741) will evaluate the safety, tolerability, and efficacy of setmelanotide over 1 year of treatment in patients aged 2 to <6 years with proopiomelanocortin deficiency, leptin receptor deficiency, or BBS

Methods

Participants and Eligibility Criteria

- VENTURE is a 1-year, open-label, Phase 3 clinical trial that will enroll ~15 eligible pediatric patients at clinical centers in North America, Europe, or Australia (Table 1)
  - Because of the rarity of the conditions investigated, the sample size was primarily determined on the basis of clinical and operational considerations. Owing to the number of patients enrolled and the single active treatment arm design, no statistical power was calculated and results will be presented descriptively
- This trial has been discussed and agreed upon with national and international regulatory authorities, including the US Food and Drug Administration and European Medicines Agency, as part of the pediatric investigational plan for setmelanotide

Table 1. Key Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
Obesity due to • POMC or LEPR deficiency obesity, confirmed by genetic testing demonstrating biallelic variants in *POMC*, *PCSK1*, or *LEPR* that are interpreted as pathogenic, likely pathogenic, or VOUS by ACMG criteria • BBS as defined by Beales criteria[8] and genetic confirmation of homozygous or compound heterozygous loss-of-function mutation in BBS genes	• HbA1c >9.0% • GFR <60 mL/min/1.73 m^2
Age 2 to <6 years at the time of informed consent	Patient or close family history of • Significant liver disease other than NAFLD or NASH • Oculocutaneous albinism • Melanoma
Obesity defined as • BMI ≥97th percentile for age and sex • Body weight ≥15 kg at the time of enrollment	Dermatologic findings related to melanoma or premelanoma skin lesions during screening
Hyperphagia symptoms or behavior	Uncontrolled endocrine, metabolic, or medical condition(s) known to impact body weight

ACMG, American College of Medical Genetics; BBS, Bardet-Biedl syndrome; BMI, body mass index; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; LEPR, leptin receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; POMC, proopiomelanocortin; VOUS, variant of uncertain significance.

Study Design

- Patients will undergo a dose escalation phase until reaching the final maintenance dose based on weight at trial entry; duration of treatment will be 52 weeks including titration (Figure)
  - Setmelanotide 0.5 mg will be administered once daily and increased by 0.5 mg every 2 weeks until the maximum dose is reached
  - The maximum setmelanotide dose will be based on weight bands for patients aged 2 to <6 years to support an exposure similar to that of adults receiving 2 to 3 mg of setmelanotide daily
    - The maximum dose for patients with body weight <20, 20 to <30, 30 to <40, and ≥40 kg will be 0.5, 1.0, 1.5, and 2.0 mg daily, respectively
  - Dose may be adjusted on the basis of safety and tolerability
  - An end-of-study visit will be conducted via telephone at Week 56

Endpoints and Analysis

- Efficacy endpoints will be reported as change from baseline to Week 52 (Table 2)

Table 2. Study Endpoints

Primary	Secondary	Exploratory
Proportion of patients with ≥0.2 reduction in BMI Z score	Mean absolute change in BMI Z score per age and sex Mean change in %BMI95 per age and sex Mean relative percent change in BMI Mean change in vital signs and laboratory evaluations Mean change in bone age Mean change in ASQ®-3 score	Pharmacokinetics Mean change in metabolic parameters Mean change in waist circumference Mean change in hunger score Mean change in caregiver burden and work productivity scores Mean change in QOL score

%BMI95, percent of the body mass index (BMI) 95th percentile; ASQ®-3, Ages and Stages Questionnaire, Third Edition; QOL, quality of life.

- Adverse events reported throughout the study will be summarized by frequency, seriousness, and severity
- Results will be reported as descriptive statistics for the safety population (ie, patients who receive ≥1 dose of setmelanotide)

Conclusions

- This 1-year, open-label, Phase 3 trial will provide safety and efficacy data for the potential early treatment of patients aged 2 to <6 years with BBS or obesity due to biallelic variants in *POMC*, *PCSK1*, or *LEPR*
- The VENTURE trial has completed enrollment

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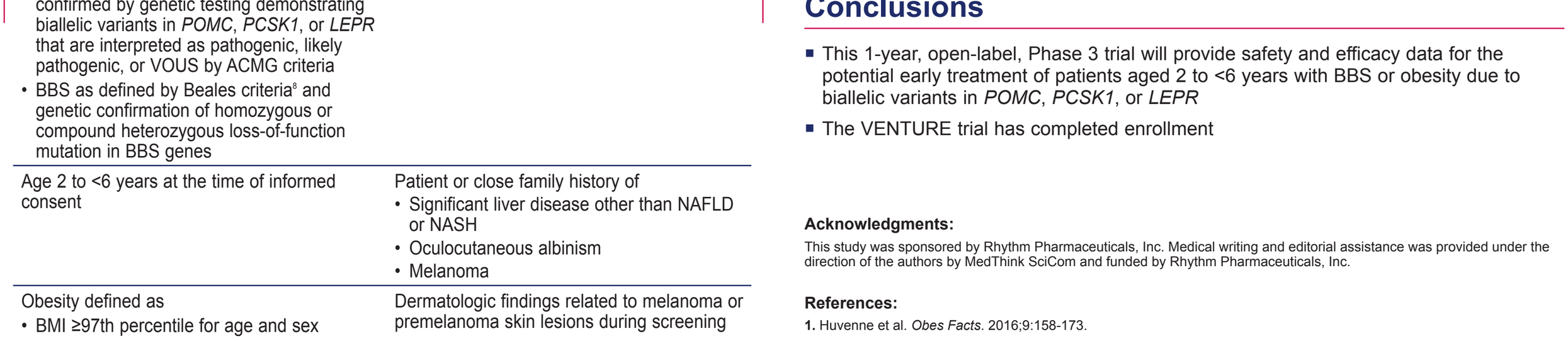
Figure. Study design.



[a]During the enrollment visit, baseline measurements will be taken (eg, patient height and weight; caregiver burden), and the caregiver will administer the first dose of setmelanotide via subcutaneous injection under study staff supervision and receive an electronic diary to record daily injection adherence. QD, once daily.