A Phase 3 Trial in Participants With Obesity Due to Bardet-Biedl Syndrome or Alström Syndrome: Efficacy and Safety of the Melanocortin 4 Receptor Agonist Setmelanotide

##

Robert Haws, MD[1]; Karine Clément, MD, PhD[2,3]; Hélène Dollfus, MD[4]; Joan C. Han, MD[5]; Andrea Haqq, MD, MHS[6]; Gabriel Á. Martos-Moreno, MD, PhD[7]; Robert S. Mittleman, MD[8]; Murray Stewart, MD[8]; Matt Webster, MS[8]; Jack A. Yanovski, MD, PhD[9]; Guojun Yuan, PhD[8]; Jesús Argente, MD, PhD[7,10]

[1]Marshfield Clinic Research Institute, Marshfield, WI, USA; [2]Assistance Publique Hôpitaux de Paris, Nutrition Department, Pitié-Salpêtrière Hospital, Paris, France; [3]Sorbonne Université, INSERM, NutriOmics Research Unit, Paris, France; [4]Hôpitaux Universitaires de Strasbourg, CARGO and Department of Medical Genetics, Strasbourg, France; [5]Lebonheur Children's Foundation Research Institute, University of Tennessee Health Science Center, Memphis, TN, USA; [6]Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada; [7]Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid, University Hospital Niño Jesús, CIBER "Fisiopatología de la obesidad y nutrición" (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain; [8]Rhythm Pharmaceuticals, Boston, MA, USA; [9]National Institutes of Health, Bethesda, MD, USA; [10]IMDEA Institute, Madrid, Spain

Presenting Author:
Robert Haws
haws.robert@marshfieldclinic.org

Summary

- **In this Phase 3 trial in participants with Bardet-Biedl syndrome (BBS) or Alström syndrome, setmelanotide was associated with significant body weight and hunger reduction, with outcomes driven by responses in individuals with BBS**
- **Setmelanotide was a well-tolerated treatment, and no new safety concerns emerged**
- **On the basis of these results, investigation into the effect of setmelanotide in other rare genetic diseases of obesity related to the melanocortin 4 receptor (MC4R) pathway is warranted**

Introduction

- In individuals with BBS or Alström syndrome, dysfunction in the MC4R pathway has been hypothesized to lead to hyperphagia and obesity[1,2]
- Setmelanotide is an MC4R agonist that was previously shown to reduce hunger and body weight in participants with BBS in an open-label Phase 2 trial[3]

Objective

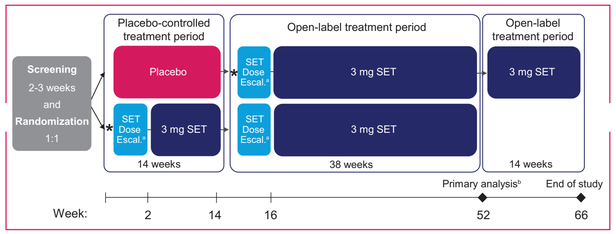
- To determine the effect of setmelanotide on weight loss, hunger reduction, and safety outcomes in individuals aged ≥6 years with obesity and a diagnosis of BBS or Alström syndrome

Methods

Study Design

- This multicenter, placebo-controlled plus open-label Phase 3 clinical trial (NCT03746522) was designed to evaluate the effect of setmelanotide on body weight and hunger in participants with BBS or Alström syndrome (Figure 1)

Figure 1. Study design.



Asterisk denotes active treatment baseline for each study group. [a]During dose escalation, participants ≥16 years of age received setmelanotide 2 mg QD for 2 weeks, participants <16 years of age received setmelanotide 1 mg QD for the first week and 2 mg for the second week, and all participants received 3 mg at the beginning of Week 3. [b]A multiple imputation model was used to impute data in participants who received <52 weeks of setmelanotide at the time of the primary analysis. Escal., escalation; QD, once daily; SET, setmelanotide.

Key Entry Criteria

- All participants had obesity and a confirmed diagnosis of BBS or Alström syndrome. Obesity was defined as body mass index (BMI) ≥30 kg/m^2 (in those aged ≥16 years) or weight >97th percentile (in those aged 6–15 years)
- Participants were excluded if they had recently experienced weight loss, had recent use of obesity medication, or ever received setmelanotide

Endpoints and Assessments

- The primary endpoint was the proportion of participants (≥12 years) who achieved ≥10% reduction in body weight from baseline after 52 weeks of setmelanotide treatment
- Key secondary endpoints further assessed changes in body weight and hunger
  - Daily maximal hunger score was based on participant responses to scoring their "most" hunger during the day using a numerical rating scale ranging from 0 to 10, where 0 = not hungry at all and 10 = the hungriest possible
- Recognizing that adolescents normally gain height and weight, an analysis was performed to assess changes in BMI Z scores in participants with BBS aged <18 years (predefined exploratory endpoint)
- For statistical analysis, the primary endpoint had binomial proportions calculated for each of the 100 multiple imputed data sets, which were combined using Rubin's Rule to compare against the null hypothesis with 95% confidence intervals (CIs) and *P* values
  - Efficacy outcomes are reported relative to active treatment baseline, which is the last measurement before the first dose of setmelanotide (ie, Week 0 for the setmelanotide group and Week 14 for the placebo group)
  - A multiple imputation model was used to impute data in participants who had received <52 weeks of setmelanotide at the time of the primary analysis

Results

Participant Disposition and Baseline Characteristics

- This trial enrolled 38 participants with confirmed BBS (n=32) or Alström syndrome (n=6; Table 1)
- 5 participants <12 years and 2 participants ≥12 years who discontinued before receiving active therapy were not included in the primary analysis

Table 1. Baseline Participant Characteristics

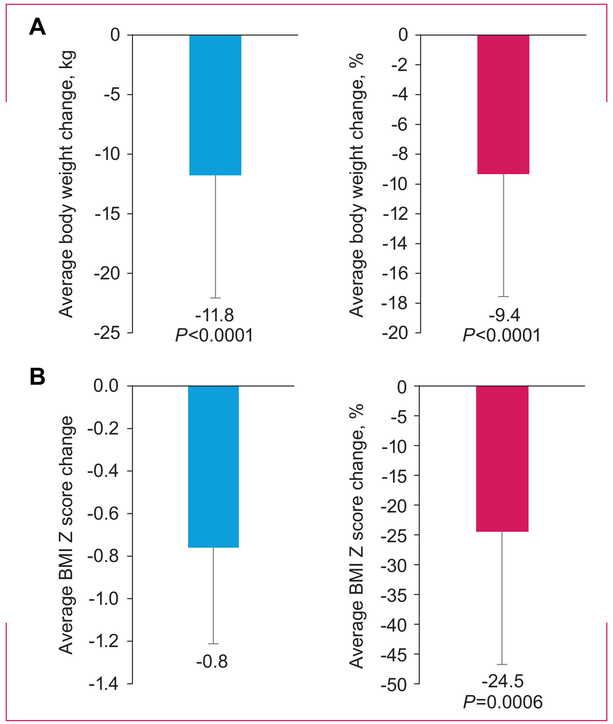
	Participants (N=38)
Randomization, n (%)	
Setmelanotide	19 (50.0)
Placebo	19 (50.0)
Genotype, n (%)	
BBS	32 (84.2)
Alström syndrome	6 (15.8)
Age, mean (SD) [range], y	19.8 (10.2) [7–44]
Male to Female ratio	15:23
Ethnicity, n (%)	
Hispanic or Latino	1 (2.6)
Not Hispanic or Latino	37 (97.4)
Weight, mean (SD) [range], kg	112.0 (31.0) [49.3–191.8][a]
BMI, mean (SD) [range], kg/m^2	42.2 (11.1) [24.4–83.0][a]

[a]Active treatment baseline, n=36. BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

Efficacy Outcomes

- After 52 weeks of treatment, in participants aged ≥12 years (n=31), 34.5% (95% CI, 17.5%–51.6%; *P*=0.0024) achieved ≥10% reduction in body weight from baseline
  - All participants achieving ≥10% reduction in body weight from baseline had BBS
- In participants aged ≥12 years (n=31), the mean ± standard deviation (SD) percent change in body weight from baseline was −6.2% ± 8.6% (*P*<0.0001)
- For participants with BBS
  - In participants aged ≥18 years (n=15), mean ± SD percent change in body weight from baseline was −9.4% ± 8.2% (Figure 2A)
  - In participants aged <18 years (n=16), the mean ± SD change from baseline in BMI Z score was −0.8 ± 0.4 (Figure 2B)

Figure 2. (A) Change in body weight among participants with BBS aged ≥18 years (n=15), and **(B)** change in BMI Z score among participants with BBS aged <18 years (n=16).[a]

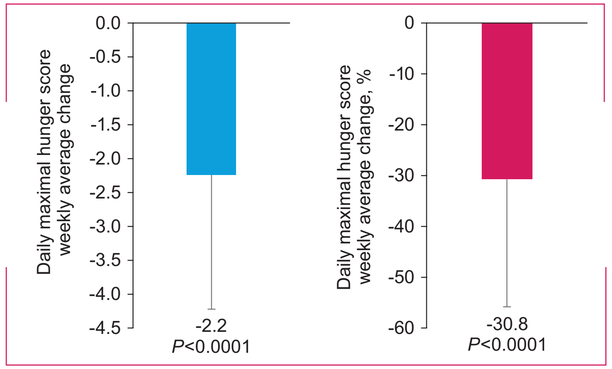


Error bars are the standard deviation. [a]Baseline, n=16 and Week 52, n=14. BBS, Bardet-Biedl syndrome; BMI, body mass index.

- In participants aged ≥12 years (n=31), mean ± SD percent change in daily maximal hunger score weekly average from baseline was −30.8% ± 25.0% among those without cognitive impairment (n=16; *P*<0.0001) (Figure 3)
- After 52 weeks of setmelanotide, in participants aged ≥12 years (n=31), 60.2% (95% CI, 35.3%–85.1%; *P*<0.0001) achieved ≥25% reduction in daily maximal hunger score weekly average from baseline
- The placebo-controlled treatment period data were supportive of the findings in this poster, but will be presented separately

Acknowledgments:
This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided under the direction of the authors by Kristin French, PhD, and David Boffa, ELS, of MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

Figure 3. Change in daily maximal hunger score in participants aged ≥12 years without cognitive impairment (n=16).



Error bars are the standard deviation.

Safety Outcomes

- The most commonly reported treatment-related adverse events (AEs) in all participants (n=38) included skin hyperpigmentation, injection site erythema, and nausea (Table 2)

Table 2. Treatment-Related AEs[a]

	Participants, n (%)
At least 1 AE	37 (97.4)
Serious AE	1 (2.6)
AE leading to study withdrawal[b]	5 (13.2)
Common AEs (≥15%)	
Skin hyperpigmentation	22 (57.9)
Injection site erythema	16 (42.1)
Injection site pain	11 (28.9)
Injection site pruritus	11 (28.9)
Injection site bruising	9 (23.7)
Injection site induration	8 (21.1)
Nausea	7 (18.4)

[a]Treatment-related treatment-emergent AEs reported; safety analysis set, N=38. [b]AEs are treatment emergent. AE, adverse event.

- There was 1 serious AE of anaphylactic reaction among all participants (n=38) that was considered related to treatment during this participant's placebo-controlled period
- AEs in all participants including nausea, vomiting, and anaphylactic reaction led 5 participants to withdraw from the trial

References:
1. Davenport et al. *Curr Biol.* 2007;17:1586-1594. **2.** Yazdi et al. *PeerJ.* 2015;3:e856. **3.** Haws et al. *Diabetes Obes Metab.* 2020;22:2133-2140.