Effect of the Melanocortin-4 Receptor Agonist Setmelanotide on Obesity and Hyperphagia in Individuals Affected by Bardet-Biedl Syndrome

RFC6.3

Robert M. Haws,[1] Kristina L. Fletty,[2] Thomas J. McIntee,[1] Clayton Green,[1] Jeremy Pomeroy,[1] Michelle Hylan,[2] Cathy Folster,[2] Elisabeth K. Davis,[3] Sheila M. Brady,[3] Fred T. Fiedorek,[2] Jack A. Yanovski[3]

[1]Marshfield Clinic Research Institute, Marshfield, WI, USA; [2]Rhythm Pharmaceuticals Inc., Boston, MA, USA; [3]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

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

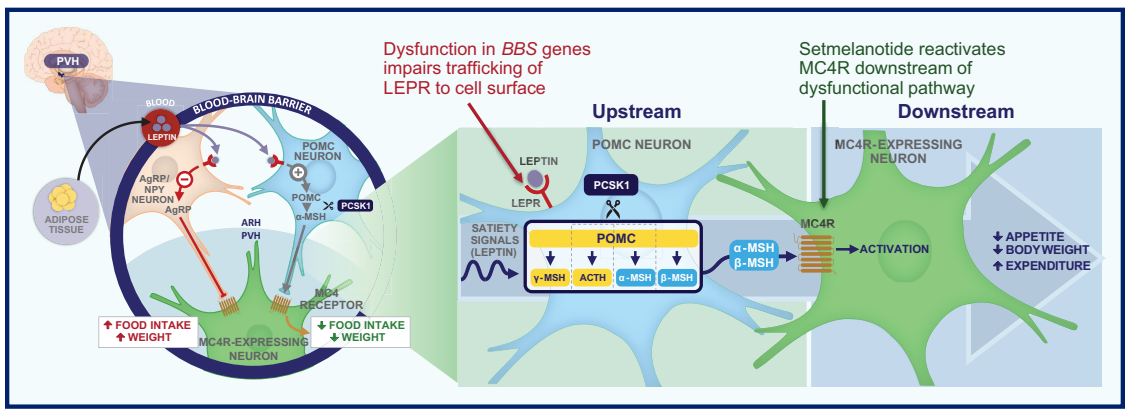
Summary

- **Updated data from the Bardet-Biedl syndrome (BBS) cohort of the phase 2 proof-of-concept basket study show a reduction in body weight and decreased appetite as shown by lower hunger scores consistent with a previous study of a rare genetic disorder of obesity[1]**
- **Setmelanotide is generally well tolerated and has a safety profile consistent with previous reports[1,2]**
- **These results support the continued evaluation of setmelanotide for treatment of obesity and hunger in people with rare genetic disorders of obesity including BBS**

Introduction

- Setmelanotide is a melanocortin-4 receptor (MC4R) agonist that reduces body weight and hunger scores in individuals affected by rare genetic disorders of obesity resulting from dysfunction of genes upstream of MC4R[1,2]
- BBS is a rare disorder characterized by early-onset severe obesity (associated with insatiable hunger [termed hyperphagia]), visual impairment, cognitive disabilities, polydactyly, renal dysfunction, and hypogonadism[3]
  - *BBS* genes are implicated in the function of the MC4R pathway, which is a component of the central melanocortin pathway (Figure 1)[2,4,5]
- The effect of setmelanotide on efficacy and safety measures in individuals with BBS is being investigated in an ongoing phase 2 study (ClinicalTrials.gov identifier: NCT03013543)
  - 12-16 week data on 5 participants have been reported elsewhere[6]
  - Additional data from 9 participants (4 new) are reported here

Figure 1. The MC4R pathway, a component of the central melanocortin pathway, regulates appetite and energy balance, and mutations in this pathway can result in rare genetic disorders of obesity.[5,7]



AgRP, agouti-related protein; ARH, arcuate nucleus; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PVH, paraventricular nucleus of hypothalamus.

Objective

- To report an update of the effect of setmelanotide on body weight, hunger scores, and safety in 9 individuals diagnosed with BBS in an ongoing phase 2 study

Methods

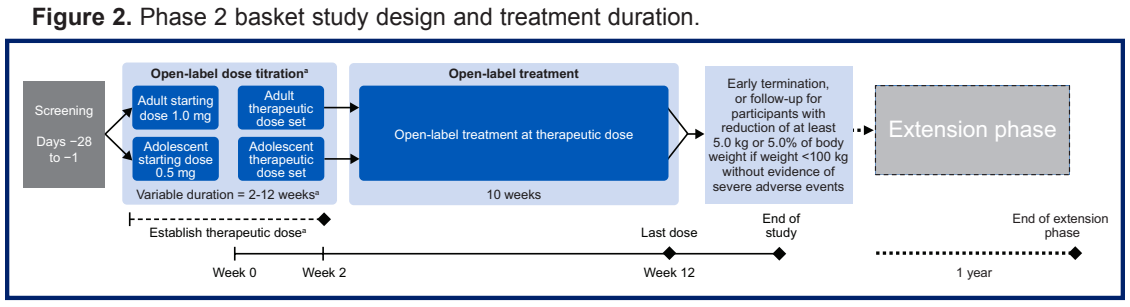
Study Participants

- This study enrolls individuals with rare genetic disorders of obesity, including BBS
  - Participants are ≥12 years of age with a body mass index (BMI) ≥30 kg/m² for those aged ≥18 years or weight >97th percentile for age/sex on a growth chart for those aged ≥12 to <18 years
  - Participants must have BBS
- Individuals with >2% weight loss from intensive diet or exercise regimens within 2 months of enrollment or >10% weight loss that was durably maintained following gastric bypass surgery are excluded

Study Design

- Setmelanotide is administered as a once-daily subcutaneous injection (Figure 2). Initial dosage in adults is 1.0 mg/day and in adolescents (≥12 to <18 years of age) is 0.5 mg/day, with dose titration by 0.5-mg increments every 2 weeks (maximum 3.0 mg)

Figure 2. Phase 2 basket study design and treatment duration.



[a]The last 2 weeks of the open-label dose titration phase in which the therapeutic dose for a participant is established is considered the first 2 weeks of the open-label treatment phase. Participants then receive an additional 10 weeks of active treatment in the open-label treatment phase for a total of 12 weeks of treatment at the therapeutic dose.

Endpoints and Assessments

- The primary endpoint is the mean percent change in body weight after 12 weeks at the therapeutic dose
- Secondary endpoints include safety and tolerability and changes in hunger rating, percent body fat, laboratory values, and waist circumference after 3 months of treatment
- Exploratory observer-related questionnaires include the food problem diary (FPD) and the significant event questionnaire (SEQ), which are completed by caregivers of individuals with cognitive impairment
  - The FPD is a 10-item observer-reported outcome measure designed to capture common food-related behaviors as recorded daily by caregivers
    - Total scores range from 0 to 30, with higher scores suggestive of more severe hyperphagia/food-related behaviors
  - The SEQ is an 8-item observer-reported outcome measure designed to capture rare food-related behaviors (ie, behaviors expected to occur only with a reduction in hyperphagia in response to treatment) as recorded weekly by caregivers
    - Total scores range from 0-8, with higher scores suggestive of more significant treatment benefit

Results

Participants and Baseline Characteristics

- As of August 2018, 9 individuals with BBS have been enrolled (median duration of study treatment: 31 weeks [range, 18-71 weeks])
  - Mean ± standard error of the mean (SEM) baseline weight among participants was 125.7 ± 3.2 kg; mean ± SEM BMI was 44.7 ± 0.5 kg/m²
  - Baseline characteristics for each participant are listed in Table 1.
- Of the 9 participants enrolled by August 2018, 8 had 12 weeks of treatment for assessment of response and 3 withdrew from the study because of lack of weight response

Table 1. Baseline Characteristics of Participants With *BBS* Mutations

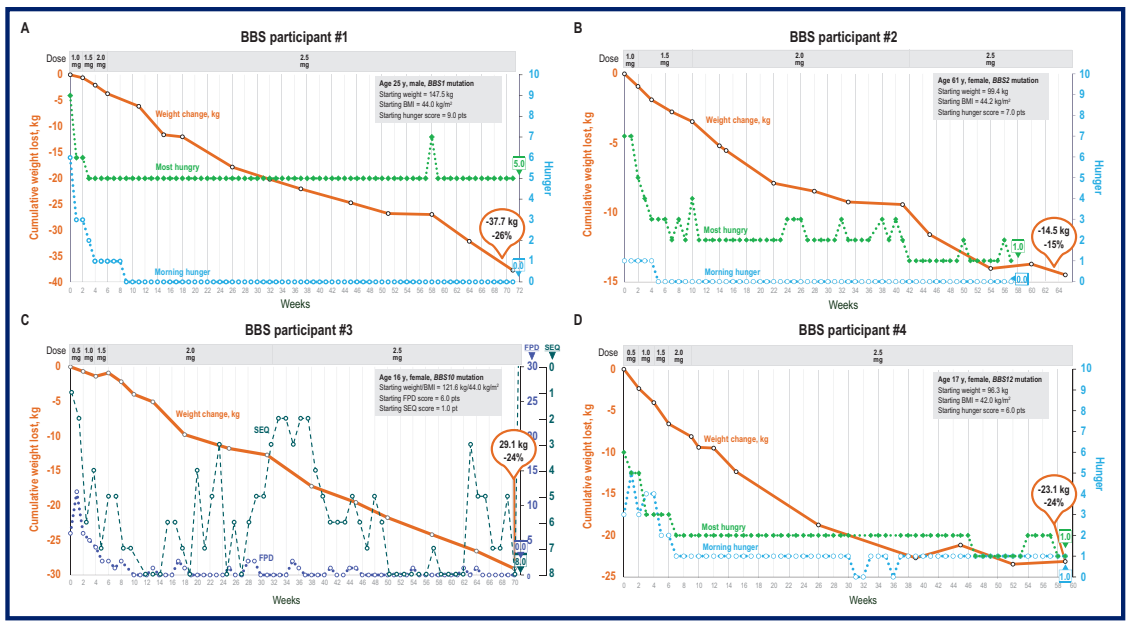
Participant	Age/Sex	Mutation	Baseline weight, kg	Baseline BMI, kg/m²	Hunger score	FPD/SEQ score[a]
1	25/M	*BBS1*	147.5	44.0	9	—
2	61/F	*BBS2*	99.4	44.2	7	—
3	16/F	*BBS10*	121.6	44.0	—	6/1
4	17/F	*BBS12*	98.3	42.0	6	—
5	12/F	*BBS1*	119.3	49.0	—	15/1
6	16/F	*BBS5*	122.3	42.8	9	—
7	14/F	*BBS4*	88.6	36.9	7	—
8[b]	13/M	Not established[c]	171.8	51.3	—	9/2
9	31/M	*BBS1*	162.7	48.1	6	—

BBS, Bardet-Biedl syndrome; BMI, body mass index; F, female; FPD, food problem diary (score range, 0-30); M, male; SEQ, significant event questionnaire (maximum score of 8 points).
[a]Completed by caregiver for individuals with cognitive difficulties. [b]Withdrew from study. [c]"Not established" means that the individual has BBS by clinical characteristics, but molecular testing has not determined definitively the abnormality causing BBS.

Efficacy

- Long-term data on body weight reductions and changes in hunger scores are shown for 4 participants in Figure 3
- Participant 5 (pediatric participant with type 1 diabetes) experienced a 53.3% reduction in hunger score and reduction in hemoglobin A1c from 10.1% to 7.6%
  - There was no change in body weight; however, there was flattening of the weight curve relative to prior childhood weight gain
  - This participant withdrew after 31 total weeks of therapy because of lack of weight loss
  - The participant gained 5.9 kg following discontinuation, and her appetite and hunger returned to baseline levels and hemoglobin A1c increased to 11.7%
- An additional 4 individuals diagnosed with BBS have been enrolled with a shorter treatment duration at the time of data cutoff
- Participant 6 had a body weight reduction of 6.8% (8.3 kg) and 66.0% reduction in hunger at 15 weeks (therapeutic dose)
- Participant 7 had a body weight reduction of 6.6% (5.8 kg) and a 21% reduction in hunger at 18 weeks
- Participant 8 and participant 9 withdrew because of a lack of weight loss

Figure 3. Weight and hunger scores over time in participants with sustained weight loss.



Results for individual participants are shown in **(A-D)**. In panel **(C)**, the green line shows the significant event questionnaire (SEQ) score, which counts significant food behavior events rarely seen in this population (answered as yes or no for 8 behaviors; a maximum score of 8 points means greatest improvement; shown in reverse scale so downward movement equals improvement), and the blue line shows the food problem diary (FPD) score (a higher score is suggestive of more severe hyperphagia or food-related behaviors). BBS, Bardet-Biedl syndrome; BMI, body mass index; pt, point.

Safety

- Adverse events included increased pigmentation of the skin/nevi and mild injection site reactions
- No clinically significant detrimental changes in blood pressure or heart rate have been reported
- No serious adverse events were reported
- No discontinuations were due to adverse events

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided by Jonathan Morgan, PhD, Ali Rosenberg, PhD, and David Boffa, ELS, MedThink SciCom, and funded by Rhythm Pharmaceuticals Inc.

References: 1. Kühnen P et al. *N Engl J Med.* 2016;375:240-246. **2.** Clement K et al. *Nat Med.* 2018;24:551-555. **3.** Huvenne H et al. *Obes Facts.* 2016;9:158-173. **4.** Seo S et al. *Hum Mol Genet.* 2009;18:1323-1331. **5.** Shen WJ et al. *Biochim Biophys Acta.* 2017;1863:2477-2485. **6.** Haws RM et al. Poster presented at: The Obesity Society Annual Meeting at ObesityWeek 2016; October 31-November 4, 2016; New Orleans, LA. **7.** Yazdi FT et al. *PeerJ.* 2015;3:e856.