3-Year Setmelanotide Outcomes in Patients With POMC/LEPR Deficiency or BBS and Obesity

2186-LB

Andrea Haqq,[1] Wendy Chung,[2] Gauri Malthankar,[3] Jill Garrison,[3] Uzoma Okorie[4]

[1]Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada; [2]Division of Molecular Genetics, Department of Pediatrics, Columbia University, New York, NY, USA; [3]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [4]Department of Pediatrics, Marshfield Clinic, Marshfield, WI, USA

Presenting Author: Gauri Malthankar, gmalthankar@rhythmtx.com

Scan to hear an audio walk through of the poster

To download a PDF version of this presentation please scan or visit https://hcp.rhythmtx.com/publications-presentations/

Background

- The hypothalamic melanocortin-4 receptor (MC4R) pathway regulates hunger, satiety, energy expenditure, and, subsequently, body weight[1-4]
- Proopiomelanocortin (POMC; including variants in *POMC* or *PCSK1*) deficiency, leptin receptor (LEPR) deficiency, and Bardet-Biedl syndrome (BBS) are associated with aberrant MC4R pathway signaling, leading to early-onset, severe obesity[5-11]
- In Phase 3 trials in these patient populations as young as 2 years old, the MC4R pathway agonist setmelanotide improved weight-related measures and hunger severity with an acceptable safety profile[8,12,13]

Objective

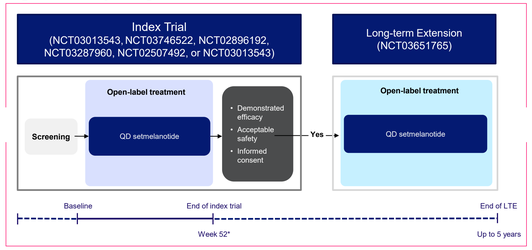
- To assess long-term weight-related outcomes and safety over ~3 years of setmelanotide treatment in patients with POMC/LEPR deficiency obesity or BBS

Methods

Trial Design

- Patients aged ≥6 years with POMC/LEPR deficiency or BBS were eligible for this long-term extension (LTE) trial (NCT03651765) if they
  - Completed a prior index trial in which they received setmelanotide
  - Experienced a highly clinically meaningful weight response (≥10% body weight [in those ≥18 years of age] or ≥0.3 body mass index [BMI] Z score [in those <18 years of age] reduction) with 1 year of treatment
- Patients were ineligible if they
  - Had recent diet or exercise regimen or recently underwent gastric bypass surgery resulting in weight loss or stabilization
  - Had significant or concerning dermatologic findings (eg, melanoma or skin lesions)
  - Had a history of suicidal ideation or behavior
  - Had moderate-to-severe renal dysfunction
  - Were considered not suitable to participate in the opinion of the study investigator
- Patients began the LTE immediately following completion of the index trial and continued on the same dose of setmelanotide (Figure 1)

Figure 1. Study Design



Data from prior index trials have been published previously.[8,12,14-16] *Not all patients received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. LTE, long-term extension; QD, once daily.

Outcomes

- Weight-related efficacy outcomes were evaluated at yearly intervals of setmelanotide treatment across the index and LTE trials in patients who had 3-year on-treatment measurements
- Adverse events (AEs) were evaluated

Results

Patient Disposition and Baseline Characteristics

- Of 62 patients entering the LTE, 44 had continuous 3-year treatment (Table 1)
- Of these 44 patients, 40 had 3-year measurements and were analyzed from index baseline
  - Three pediatric patients had transitioned to adulthood, and 1 adult patient had their 3-year measurement missing

Table 1. Baseline Characteristics of Patients With Continuous 3-Year Treatment

	POMC/LEPR (n=19)	BBS (n=25)
Age, mean (SD; range), y	20.2 (6.7; 10-36)	21.4 (13.62; 7-61)
Age range, n (%)		
≥18 y	11 (57.9)	10 (40.0)
<18 y	8 (42.1)	15 (60.0)
Sex, n (%)		
Male	9 (47.4)	9 (36.0)
Female	10 (52.6)	16 (64.0)
Race		
White	13 (68.4)	22 (88.0)
Other	6 (31.6)	3 (12.0)
Weight, mean (SD), kg	133.4 (32.6)	108.3 (29.2)
BMI, mean (SD), kg/m^2	45.8 (10.1)	41.7 (9.2)
BMI Z score, mean (SD)*	3.2 (0.5)	3.1 (1.4)
%BMI95, mean (SD), percentage points*	152.7 (16.0)	147.2 (37.0)
Waist circumference, mean (SD), cm	127.2 (19.1)	115.3 (18.7)

%BMI95, percent of the 95th BMI percentile; BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation. *Calculated using the Centers for Disease Control and Prevention (CDC) 2022 methodology for children (aged <18 years) only (n=23).

Safety Outcomes

- Safety profiles were consistent with index trials; no new safety signals were observed in the LTE (Table 2)

Table 2. AEs Occurring During the Index and LTE Trials in the Safety Population

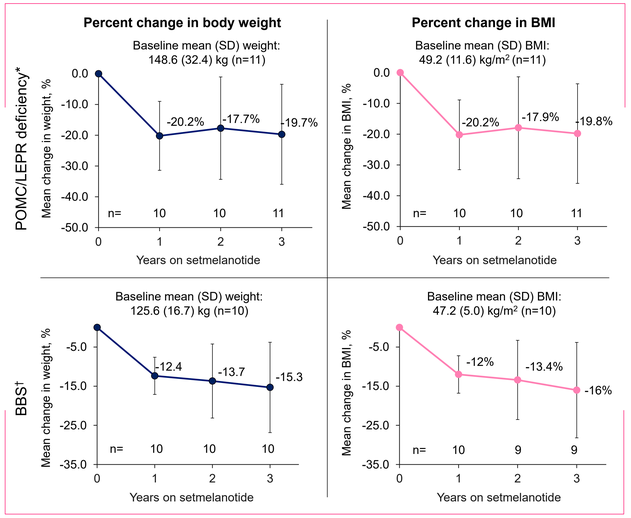
	POMC/LEPR, n (%) (N=24)*	BBS, n (%) (N=54)†
Any AEs	24 (100.0)	54 (100)
Any treatment-related AEs	24 (100.0)	54 (100)
Serious treatment-related AEs	0 (0.0)	1 (1.9)
AEs leading to study drug discontinuation	1 (4.2)	4 (7.4)
AEs reported in ≥25% of the population		
Injection site reactions‡,§	23 (95.8)	
Injection site erythema	–	30 (55.6)
Injection site pruritus	–	27 (50.0)
Injection site bruising	–	21 (38.9)
Injection site induration	–	20 (37.0)
Injection site pain	–	16 (29.6)
Other disorders‡,‖	22 (91.7)	-
AEs reported in ≥25% of the population (cont)		
Skin hyperpigmentation‡,¶	22 (91.7)	36 (66.7)
Nausea	17 (70.8)	19 (35.2)
Diarrhea	12 (50.0)	13 (24.1)
Mood disorders‡,#	11 (45.8)	–
Abdominal pain, upper	8 (33.3)	–
Abdominal pain	7 (29.2)	–
Vomiting	7 (29.2)	17 (31.5)
Gastroenteritis	6 (25.0)	–
Spontaneous penile erection**	5 (33.3)	–
Headache	Included as "other"	14 (25.9)

AE, adverse event; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin. *Data as of October 4, 2022; values represent a data cut of patients with ≥3 years of data at the time of analysis. †Data as of October 29, 2022; includes all patients enrolled in the index and LTE trials and represents an earlier data cut than efficacy data. ‡If a patient experienced >1 event with a given AE group, that patient is counted only once for that AE group. §Injection site reactions include injection site erythema, injection site edema, injection site pruritus, injection site induration, injection site pain, injection site bruising, and injection site reaction. ‖Other disorders include headache, upper respiratory tract infection, back pain, arthralgia, dry mouth, asthenia, fatigue, pain in extremity, alopecia, dizziness, pyrexia, vertigo, chills, dry skin, influenza, nasopharyngitis, and oropharyngeal pain. ¶Skin hyperpigmentation includes skin hyperpigmentation and melanocytic nevus. #Mood disorders are depressed mood and suicidal ideation. Most mood disorder events were reported in patients with a history of psychiatric disease and were considered not or unlikely related to study drug. **Percentage of male patients (n=15).

Efficacy Outcomes

- Adult patients experienced decreases in body weight and BMI with 1 year of treatment, which was maintained through Year 3 (Figure 2)

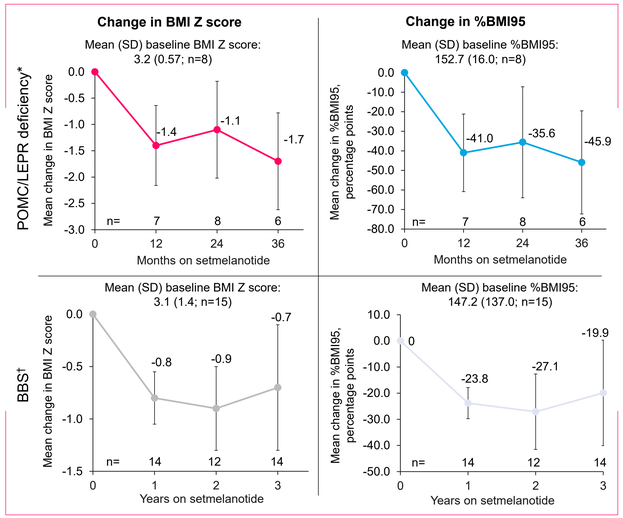
Figure 2. Mean Percent Change in Body Weight and BMI Among Adult Patients (≥18 Years of Age)



BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation. Error bars are the SD. *Population may increase over time because of missing data points at earlier time points. †One patient with BBS had missing BMI at years 2 and 3.

- Pediatric patients experienced decreases in age-appropriate weight-related measures with 1 year of treatment, which was maintained through Year 3 (Figure 3)

Figure 3. Mean Percent Change in BMI Z Score and %BMI95 in Pediatric Patients (<18 Years of Age)



%BMI95, percent of the 95th BMI percentile; BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation. Error bars are the SD. *Population may increase over time because of missing data points at earlier time points. †One patient with BBS had missing BMI at years 2 and 3.

Conclusions

- One year of treatment with the MC4R agonist setmelanotide was associated with a clinically meaningful decrease in age-appropriate weight-related measures in both pediatric and adult patients with POMC/LEPR deficiency or BBS that was sustained with 3 years of treatment
- No new safety concerns emerged with long-term treatment
- Limitations include the lack of a control group and small sample sizes
- These findings support continuous treatment with setmelanotide in patients with obesity due to POMC/LEPR deficiency or BBS

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Medical writing and editorial assistance was provided under the direction of the authors by Fingerpaint Medical and funded by Rhythm Pharmaceuticals, Inc.

References: 1. da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **2.** Farooqi and O'Rahilly. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **3.** Vaisse et al. *Cold Spring Harb Perspect Biol*. 2017;9:a028217. **4.** Yazdi et al. *PeerJ*. 2015;3:e856. **5.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **6.** Clément et al. *Physiol Behav*. 2020;227:113134. **7.** Forsythe et al. *Front Pediatr*. 2018;6:23. **8.** Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10:859-868. **9.** Melluso et al. *Ther Clin Risk Manag*. 2023;19:115-132. **10.** Guo et al. *Diabetes*. 2019;68:1591-1603. **11.** Seo et al. *Hum Mol Genet*. 2009;18:1323-1331. **12.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **13.** Argente et al. *Lancet Diabetes Endocrinol*. 2025;13:29-37. **14.** Clément et al. *Nat Med*. 2018;24:551-555. **15.** Kühnen et al. *N Engl J Med*. 2016;375:240-246. **16.** Haws et al. *Diabetes Obes Metab*. 2020;22:2133-2140.

Previous presentation information: Data in this poster were previously presented at ObesityWeek; October 14-17, 2023; Dallas, TX (oral presentation and poster) and European Childhood Obesity Group (ECOG) Congress; October 8-10, 2024; Ghent, Belgium.