Weight Reduction After 6 Months of Oral Bivamelagon in Acquired Hypothalamic Obesity

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Introduction

- Hypothalamic melanocortin-4 receptor (MC4R) signaling is critical in the regulation of hunger, satiety, and body weight[1]
- Hypothalamic injury due to suprasellar brain tumors or surgical resection of those tumors, traumatic brain injury, and/or inflammation, can disrupt MC4R signaling, resulting in accelerated and sustained weight gain, and ultimately, acquired hypothalamic obesity (aHO)[2,3]
- MC4R agonism has been shown to be an effective treatment strategy for patients with aHO; setmelanotide, an earlier-generation, daily injectable MC4R agonist, exhibited body mass index (BMI) and hunger reductions in a 1-year Phase 3 trial in participants with aHO[4]
- In a Phase 2 double-blind trial with the oral MC4R agonist bivamelagon in aHO, there were dose-related BMI reductions from baseline to Week 14 across the 200-, 400-, and 600-mg doses[5]
  - Most participants that received placebo exhibited an increase in BMI from baseline to Week 14

Objectives

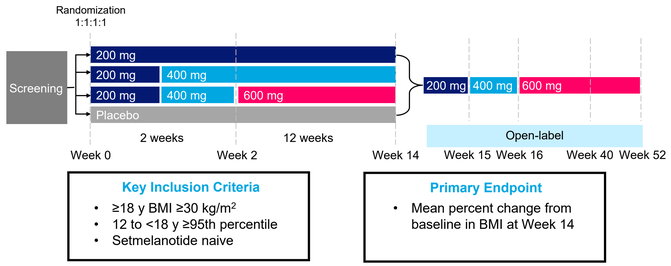
- To evaluate the safety and efficacy of 6 months of bivamelagon treatment in participants with aHO

Methods

Study Design

- Twenty-eight participants aged ≥12 years with BMI ≥95th percentile (for those aged 12 to <18 years) or BMI ≥30 kg/m^2 (for those aged ≥18 years) with aHO following hypothalamic tumor, lesion, or injury were randomized 1:1:1:1 to once-daily oral bivamelagon 200, 400, or 600 mg or placebo for 14 weeks (NCT06046443; Figure 1)

Figure 1. Study Design



BMI, body mass index.

- The primary endpoint of the trial was mean percent change from baseline in BMI at Week 14
  - Twenty-seven participants completed the double-blind period, and all bivamelagon cohorts exhibited a significantly greater percent BMI reduction versus placebo
- Participants demonstrating adequate safety/tolerability and who would benefit from initiating or continuing bivamelagon could proceed into the open-label extension (OLE) phase and receive bivamelagon 600 mg for up to 38 weeks
- All participants continuing into the OLE were retitrated from 200 mg up to a maximum of 600 mg bivamelagon, as tolerability allowed, to preserve double blinding

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References: 1. Kühnen et al. *Trends Mol Med*. 2019;25(2):136-148. **2**. Rose et al. *Obesity (Silver Spring)*. 2018;26(11):1727-1732. **3**. Roth CL, McCormack SE. *Diabetes Obes Metab*. 2024;26(suppl 2):34-45. **4**. Phillips et al. Oral presentation at: 107th Annual Meeting & Expo of The Endocrine Society; July 12-15, 2025; San Francisco, CA. **5**. Thaker et al. Poster presented at: 107th Annual Meeting & Expo of The Endocrine Society; July 12-15, 2025; San Francisco, CA.

Results

Baseline Demographics and Clinical Characteristics

- Baseline characteristics were similar between treatment groups (N=28 overall; Table 1)

Table 1. Baseline Demographics and Clinical Characteristics

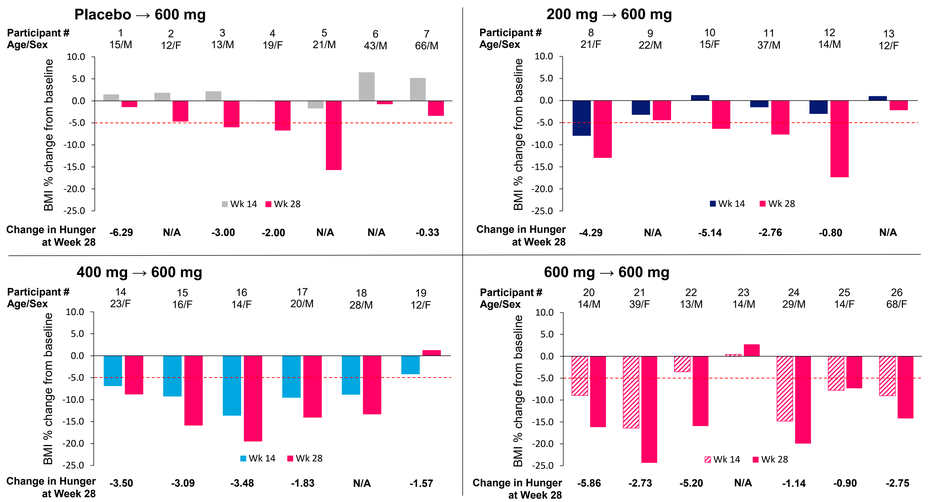
	Placebo (n=7)	Bivamelagon QD 200 mg (n=6)	Bivamelagon QD 400 mg (n=7)	Bivamelagon QD 600 mg (n=8)
Age, mean (SD), y	27.0 (20.2)	20.2 (9.2)	21.0 (8.0)	31.9 (23.0)
Sex, n (%)				
Male	4 (57.1)	3 (50.0)	3 (42.9)	5 (62.5)
Female	3 (42.9)	3 (50.0)	4 (57.1)	3 (37.5)
Race, n (%)				
White	6 (85.7)	6 (100.0)	5 (71.4)	5 (62.5)
Asian	0	0	2 (28.6)	1 (12.5)
Black or African American	1 (14.3)	1 (16.7)	0	1 (12.5)
Not reported	0	0	0	1 (12.5)
Ethnicity, n (%)				
Not Hispanic or Latino	5 (71.4)	6 (100.0)	7 (100.0)	6 (75.0)
Hispanic or Latino	2 (28.6)	0	0	2 (25.0)
Hypothalamic involvement, n (%)				
Bilateral	5 (71.4)	3 (50.0)	1 (14.3)	4 (50.0)
Unilateral	0	1 (16.7)	2 (28.6)	2 (25.0)
Unknown	2 (28.6)	2 (33.3)	4 (57.1)	2 (25.0)
Weight, mean (SD), kg	108.0 (42.3)	118.0 (35.6)	103.0 (29.3)	106.2 (22.4)
Waist circumference, mean (SD), cm	113.4 (20.3)	119.9 (14.4)	112.8 (22.7)	119.4 (20.9)
BMI, mean (SD), kg/m^2	37.0 (7.7)	38.0 (6.2)	37.7 (9.0)	41.4 (10.7)
Weekly average of the maximal daily hunger score, mean (SD)	7.9 (1.9)	7.8 (1.8)	6.7 (1.4)	6.5 (1.0)
Participants aged <18 y, n	3	3	3	4
BMI Z score, mean (SD)	3.15 (1.4)	2.99 (0.5)	2.42 (0.6)	3.74 (1.8)
%BMI95, mean % (SD)	130.8 (36.5)	126.0 (14.7)	110.8 (13.5)	145.6 (48.1)

%BMI95, percent of the body mass index 95th percentile; BMI, body mass index; QD, once daily; SD, standard deviation.

Efficacy

- The mean change from baseline in BMI at Week 28 was −5.5% (placebo→600 mg bivamelagon; n=7), −8.5% (200→600 mg; n=6), −11.7% (400→600 mg; n=6), and −13.6% (600→600 mg; n=7)
- Most participants (18/26) experienced ≥5% BMI reduction at Week 28 across all cohorts (Figure 2)

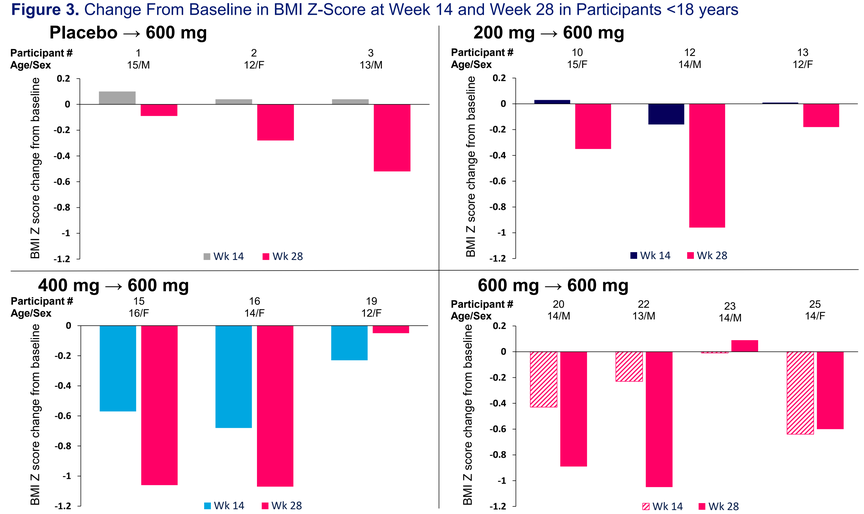
Figure 2. Percent Change From Baseline in BMI at Week 14 and Week 28



BMI, body mass index; F, female; M, male; N/A, not available; Wk, week.

- In 13 pediatric participants, the mean BMI Z score change from baseline was −0.30 for placebo→600 mg bivamelagon (n=3), −0.50 for 200→600 mg (n=3), −0.73 for 400→600 mg (n=3), and −0.61 for 600→600 mg (n=4; Figure 3)

Figure 3. Change From Baseline in BMI Z-Score at Week 14 and Week 28 in Participants <18 years



BMI, body mass index; F, female; M, male; N/A, not available; Wk, week.

- The mean change from baseline in the weekly average of the maximal daily hunger score at Week 28 was -2.90 (placebo→600 mg bivamelagon; n=4), -3.25 (200→600 mg; n=4), -2.69 (400→600 mg; n=5), and -3.10 (600→600 mg; n=6)

Safety

- The most commonly reported adverse events in all participants were vomiting (42.3%), nausea (38.5%), and diarrhea (26.9%; Table 2)

Table 2. Safety

	PBO→600 mg (n=7)	200 mg→600 mg (n=6)	400 mg→600 mg (n=6)	600 mg→600 mg (n=7)	All participants (n=26)
AE category, n (%)					
Any AE	7 (100)	5 (83.3)	5 (83.3)	5 (71.4)	22 (84.6)
Serious AEs	0	0	1 (16.7)	1 (14.3)	2 (7.7)
Treatment-related AEs	7 (100)	5 (83.3)	5 (83.3)	2 (28.6)	19 (73.1)
Treatment-related serious AEs	0	0	0	0	0
Grade ≥3 AE	0	1 (16.7)	1 (16.7)	1 (14.3)	3 (11.5)
AEs leading to study drug discontinuation	0	0	0	0	0
Most common (≥10% in BIVA overall), n (%)					
Vomiting	5 (71.4)	3 (50.0)	3 (50.0)	0	11 (42.3)
Nausea	4 (57.1)	3 (50.0)	3 (50.0)	0	10 (38.5)
Diarrhea	3 (42.9)	2 (33.3)	1 (16.7)	1 (14.3)	7 (26.9)
Headache	3 (42.9)	1 (16.7)	2 (33.3)	0	6 (23.1)
Abdominal pain	3 (42.9)	0	1 (16.7)	0	4 (15.4)
Melanocytic naevus	1 (14.3)	2 (33.3)	1 (16.7)	0	4 (15.4)
Skin hyperpigmentation	1 (14.3)	2 (33.3)	0	0	3 (11.5)

Safety data are reported in the 14-week OLE for all participants who entered the OLE and received ≥1 dose of study treatment.
AE, adverse event; BIVA, bivamelagon; OLE, open-label extension; PBO, placebo.

Conclusions

- Following the initial 14-week double-blind period, the 14-week OLE resulted in reduced weight-related measures and clinically meaningful changes in hunger score across the original bivamelagon cohorts and placebo cohorts, with acceptable tolerability
- These additional data at Month 6 continue to show robust benefits of bivamelagon on weight-related measures and hunger in participants with aHO
- A Phase 3 trial with bivamelagon in participants with aHO is currently being planned

Conflict of Interest: VT's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. EKG's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc., and has done consulting for Rhythm Pharmaceuticals. FE's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. MK's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. RM's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. EHH's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. H-WG's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. JG, JO, and H-ML are employees of Rhythm Pharmaceuticals, Inc. and have company-awarded RSU and options. ZM's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. SF's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc.