Weight Reduction After 1 Year of Oral Bivamelagon in Acquired Hypothalamic Obesity

Vidhu Thaker,[1] Ellen K. Grishman,[2] Feyza Erenler,[3] Megan M. Kelsey,[4] Ryan Morgan,[5] Elizabeth Hackman Harris,[6] Hoong-Wei Gan,[7] Julia Oosterom,[8] Hak-Myung Lee,[8] Zainaba Mohamed,[9] and I. Sadaf Farooqi[10] on behalf of the Trial Group

[1]Columbia University, New York, NY, USA; [2]St. Jude Children's Research Hospital, Memphis, TN, USA; [3]Tufts Medical Center, Boston, MA, USA; [4]Children's Hospital Colorado, Aurora, CO, USA; [5]Lynn Health Science Institute, Oklahoma City, OK, USA; [6]University of North Carolina, Chapel Hill, NC, USA; [7]Great Ormond Street Hospital for Children, London, UK; [8]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [9]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; [10]University of Cambridge, Cambridge, UK

#MON-732

Scan here for PDF

Background

- Hypothalamic melanocortin-4 receptor (MC4R) signaling plays a central role in the regulation of hunger, satiety, and body weight[1]
- Hypothalamic injury can disrupt MC4R signaling, leading to acquired hypothalamic obesity (aHO), which is characterized by hyperphagia (insatiable, pathological hunger), reduced energy expenditure, and accelerated, sustained weight gain[2-5]
- In a double-blind, Phase 2 trial with the oral MC4R agonist bivamelagon in participants with aHO, there were dose-related reductions in body mass index (BMI) observed from baseline to Week 14, the primary endpoint, across the 200-, 400-, and 600-mg dose groups, compared with BMI increases with placebo[6]

Objectives

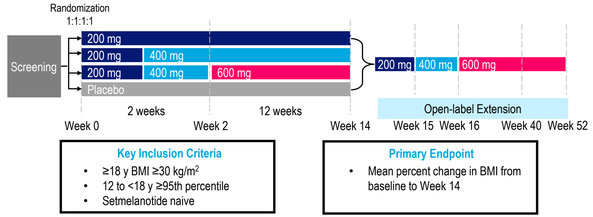
- To evaluate the efficacy and safety of bivamelagon after 1 year of treatment in participants with aHO, including an initial 14-week double-blind period followed by a 38-week open-label extension (OLE)

Methods

Study Design

- Participants aged ≥12 years with aHO following hypothalamic tumor, lesion, or injury and BMI ≥95th percentile for those aged 12 to <18 years or BMI ≥30 kg/m^2 for those aged ≥18 years were randomized 1:1:1:1 to receive 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; y, years.

- The primary endpoint of the trial was mean percent change in BMI from baseline to Week 14
- Participants without investigator-identified safety concerns were eligible to enter the OLE and receive bivamelagon 600 mg for 38 weeks
- To preserve blinding to the original double-blind treatment assignment, all participants entering the OLE were retitrated from 200 mg to a maximum dose of 600 mg bivamelagon, as tolerated

Disclosures: VT's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. and VT has received support from the National Institutes of Health. EKG's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc. and has done consulting for Rhythm Pharmaceuticals, Inc. 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., and RM is a consultant for Madrigal, Novo Nordisk, and Rhythm Pharmaceuticals, Inc., is a faculty speaker for Eli Lilly, and is a speaker for 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. 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. ISF's institution has received funding for clinical trials from Rhythm Pharmaceuticals, Inc., ISF has received payment for lectures from Rhythm Pharmaceuticals and is supported by the Wellcome Trust, Botnar Fondation, a NIHR Senior Investigator Award, and the Bernard Wolfe Endowment.

Results

Baseline Demographics and Clinical Characteristics

- Twenty-eight participants were randomized across four treatment groups
- Baseline demographics and clinical characteristics were similar across groups (Table 1)

Week 14 Efficacy

- Mean BMI change from baseline to Week 14 was dose-dependent: +2.2% (placebo), −2.7% (200 mg bivamelagon), −7.7% (400 mg bivamelagon), and −9.3% (600 mg bivamelagon) (last observation carried forward)
- Mean change in weekly most hunger score from baseline was −0.8 (placebo), −2.1 (200 mg bivamelagon), −2.8 (400 mg bivamelagon), and −2.8 (600 mg bivamelagon)

Week 52 Efficacy

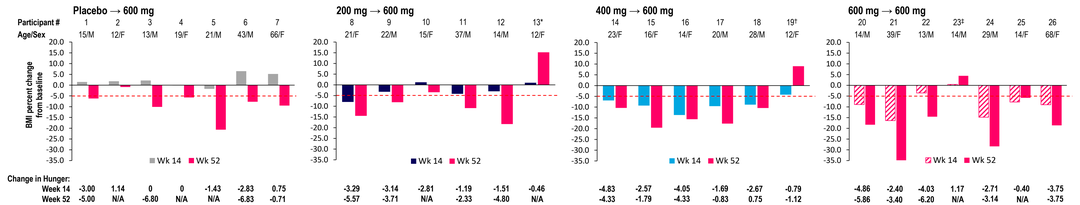
- Twenty-six participants entered the OLE and had Week 52 data available for analysis
- Mean BMI change from baseline to Week 52 was −8.7% (placebo→600 mg bivamelagon; n=7), −6.7% (200→600 mg; n=6), −10.8% (400→600 mg; n=6), and −16.6% (600→600 mg; n=7)
- Overall, 21 of 26 participants experienced a ≥5% BMI reduction at Week 52 across all treatment groups (Figure 2)
- Mean change in weekly most hunger score from baseline to Week 52 was −4.8 (placebo→600 mg bivamelagon; n=7), −4.1 (200→600 mg; n=6), −1.9 (400→600 mg; n=6), and −4.5 (600→600 mg; n=7)
- Among 13 pediatric participants, mean BMI z-score change from baseline to Week 52 was −0.51 (placebo→600 mg bivamelagon; n=3), −0.22 (200→600 mg; n=3), −0.69 (400→600 mg; n=3), and −0.62 (600→600 mg; n=4; Figure 3)

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)	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)	7 (100)	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/m²	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)

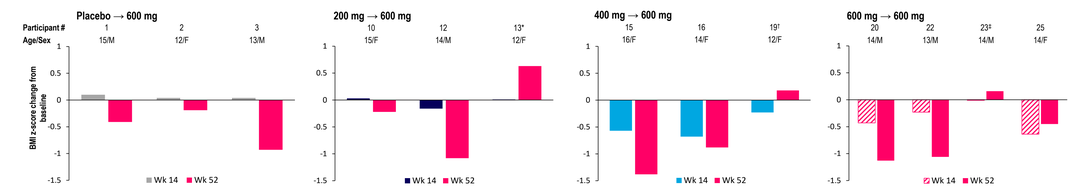
%BMI95, percent of the body mass index 95th percentile; BMI, body mass index; QD, once daily; SD, standard deviation.

Figure 2: Percent Change From Baseline in BMI at Week 14 and Week 52



*Participant 13 discontinued treatment at Wk 28 but was retained in the study through Wk 52. †Participant 19 had documented low compliance during the OLE. ‡Participant 23 had documented low compliance during the OLE.
BMI, body mass index; F, female; M, male; N/A, not available; Wk, week.

Figure 3: Change From Baseline in BMI z-Score at Week 14 and Week 52 in Participants <18 years



*Participant 13 discontinued treatment at Wk 28 but was retained in the study through Wk 52. †Participant 19 had documented low compliance during the OLE. ‡Participant 23 had documented low compliance during the OLE.
BMI, body mass index; F, female; M, male; N/A, not available; Wk, week.

Safety

- Common adverse events (AEs; ≥25%) during 38 weeks of OLE bivamelagon, across all participants, were vomiting (53.8%), nausea (46.2%), diarrhea (34.6%), and headache (26.9%; Table 2)
  - Of participants with those AEs, >70% were Grade 1 AEs

Table 2: Safety

	PBO→600 mg DB Wk 0-Wk 14 (n=7)	PBO→600 mg OLE Wk 14-Wk 52 (n=7)	200 mg→600 mg DB Wk 0-Wk 14 (n=6)	200 mg→600 mg OLE Wk 14-Wk 52 (n=6)	400 mg→600 mg DB Wk 0-Wk 14 (n=7)	400 mg→600 mg OLE Wk 14-Wk 52 (n=6)	600 mg→600 mg DB Wk 0-Wk 14 (n=8)	600 mg→600 mg OLE Wk 14 -Wk 52 (n=7)	Overall DB (BIVA only) Wk 0-Wk 14 (n=21)	Overall OLE Wk 14-Wk 52 (n=26)
Any AE	6 (85.7)	7 (100)	6 (100)	6 (100)	7 (100)	5 (83.3)	8 (100)	7 (100)	21 (100)	25 (96.2)
Grade ≥3 AE	2 (28.6)	0	0	2 (33.3)	2 (28.6)	1 (16.7)	0	2 (28.6)	2 (9.5)	5 (19.2)
Serious AEs	1 (14.3)	0	0	2 (33.3)	1 (14.3)	1 (16.7)	0	1 (14.3)	1 (4.8)	4 (15.4)
Treatment-related AEs	3 (42.9)	7 (100)	6 (100)	5 (83.3)	7 (100)	5 (83.3)	8 (100)	4 (57.1)	21 (100)	21 (80.8)
Treatment-related serious AEs	0	0	0	0	1 (14.3)	0	0	0	1 (4.8)	0
AEs leading to study drug discontinuation	1 (14.3)	0	0	0	1 (14.3)	0	0	0	1 (4.8)	0
AEs in ≥10% of participants in BIVA overall during OLE, n (%)										
Vomiting	2 (28.6)	5 (71.4)	2 (33.3)	4 (66.7)	4 (57.1)	4 (66.7)	4 (50.0)	1 (14.3)	10 (47.6)	14 (53.8)
Nausea	2 (28.6)	4 (57.1)	6 (100)	4 (66.7)	5 (71.4)	3 (50.0)	4 (50.0)	1 (14.3)	15 (71.4)	12 (46.2)
Diarrhea	1 (14.3)	3 (42.9)	2 (33.3)	3 (50.0)	5 (71.4)	2 (33.3)	3 (37.5)	1 (14.3)	10 (47.6)	9 (34.6)
Headache	2 (28.6)	3 (42.9)	1 (16.7)	1 (16.7)	5 (71.4)	2 (33.3)	1 (12.5)	1 (14.3)	7 (33.3)	7 (26.9)
Abdominal pain	0	3 (42.9)	1 (16.7)	0	2 (28.6)	1 (16.7)	1 (12.5)	1 (14.3)	4 (19.0)	5 (19.2)
Melanocytic naevus	0	1 (14.3)	1 (16.7)	2 (33.3)	0	1 (16.7)	0	0	1 (4.8)	4 (15.4)
Skin hyperpigmentation	1 (14.3)	2 (28.6)	0	2 (33.3)	1 (14.3)	0	0	0	1 (4.8)	4 (15.4)
Nasopharyngitis	1 (14.3)	0	1 (16.7)	1 (16.7)	2 (28.6)	2 (33.3)	0	1 (14.3)	3 (14.3)	4 (15.4)
Fatigue	0	1 (14.3)	1 (16.7)	0	2 (28.6)	2 (33.3)	1 (12.5)	0	4 (19.0)	3 (11.5)
Abdominal pain upper	1 (14.3)	2 (28.6)	0	0	1 (14.3)	1 (16.7)	1 (12.5)	0	2 (9.5)	3 (11.5)

Safety data are reported in the 38-week OLE for all participants who entered the OLE and received ≥1 dose of study treatment.
AE, adverse event; BIVA, bivamelagon; DB, double-blind; OLE, open-label extension; PBO, placebo.

Conclusions

- Open-label treatment with bivamelagon 600 mg for 1 year in participants with aHO resulted in progressive reductions in weight-related and hunger measures across the original bivamelagon cohorts, with acceptable tolerability
- Although most participants in the original placebo cohort gained weight during the initial 14-week placebo-controlled period, BMI decreased over the subsequent 38 weeks after initiation of bivamelagon 600 mg
- These sustained BMI and hunger reductions support further evaluation of bivamelagon in a double-blind, placebo-controlled Phase 3 trial

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

References: 1. Kühnen P, et al. *Trends Mol Med*. 2019;25(2):136-148. **2.** Rose SR, et al. *Obesity (Silver Spring)*. 2018;26(11):1727-1732. **3.** Argente J, et al. *Rev Endocr Metab Disord*. 2025;26(6):917–935. **4.** Roth CL, et al. *Metabolism*. 2010;59(2):186-194. **5.** Roth CL, et al. *Pediatr Res*. 2007;61(4):496-501. **6.** Thaker V, et al. Poster presented at: 107th Annual Meeting & Expo of The Endocrine Society; July 12-15, 2025; San Francisco, CA.