Efficacy and Safety of Once-Daily Oral Bivamelagon in Acquired Hypothalamic Obesity: Results From a Double-blind, Multicenter, Placebo-Controlled, Randomized Phase 2 Trial

SAT-711

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Introduction

- Melanocortin-4 receptor (MC4R) signaling in the hypothalamus plays a critical role in the regulation of hunger, satiety, and body weight[1]
- Damage to the hypothalamus due to injury, benign or malignant lesion, radiation, surgery, or inflammation can disrupt signaling through the MC4R pathway, resulting in accelerated and sustained weight gain and acquired hypothalamic obesity (aHO)[2-4]
  - aHO is also characterized by hyperphagia (insatiable hunger and abnormal food-seeking behaviors), reduced resting energy expenditure, decreased quality of life, higher risk of developing cardiovascular and endocrine dysfunction–related comorbidities, and higher mortality risk[5-9]
  - There are currently no approved treatments for aHO
- The favorable results from the Phase 3 trial of the injectable MC4R agonist setmelanotide suggest that this mechanism of action has therapeutic utility in aHO[10]
- Bivamelagon (BIVA, LB54640), a once-daily next-generation small molecule oral MC4R agonist, demonstrated dose-dependent weight reduction and safety in a Phase 1 first-in-human trial in healthy participants with overweight or obesity[11]
  - As an oral therapy, bivamelagon may provide a useful alternative for participants with a lower tolerance for injectable therapies

Objectives

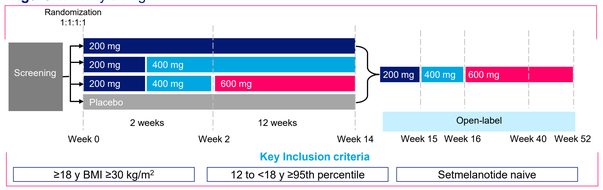
- To investigate the efficacy and safety of bivamelagon in a 14-week, multicenter, international, randomized, double-blind, placebo-controlled Phase 2 trial in participants with aHO (NCT06046443)

Methods

Trial Design

- A total of 28 participants aged ≥12 years with body mass index (BMI) ≥95th percentile (aged 12 to <18 years) or ≥30 kg/m^2 (aged ≥18 years) with aHO following hypothalamic tumor, lesion, or injury were enrolled
- Participants were randomized 1:1:1:1 to bivamelagon low (200 mg), middle (400 mg), or high (600 mg) dose or placebo for 14 weeks (all oral and once daily; Figure 1)

Figure 1. Study Design



- Eligible participants (who demonstrated adequate safety/tolerability, and, in the opinion of the investigator, would benefit from initiating or continuing treatment with bivamelagon) could proceed into the open-label extension (OLE) phase 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

Outcomes

- The primary endpoint was mean percent change from baseline in BMI at Week 14 – analysis of covariance, missing values were calculated by multiple imputation method, in the modified intent-to-treat cohort
- Secondary endpoints included mean change in BMI, percentage of participants with ≥5% reduction in body weight, and mean change in the "most hunger" score

Results

Baseline Characteristics

- Overall, 46.4% were female, the mean (standard deviation [SD]; range) age at baseline was 25.4 (16.8; 12-68) years (13 of 28 were aged <18 years), the mean (SD) BMI was 38.7 (8.4) kg/m^2, and the mean (SD) BMI Z score (in those aged <18 years) was 3.13 (1.21; Table 1)
- The most common cause of aHO was craniopharyngioma (82.1%), and the mean (SD) time from confirmed hypothalamic injury to enrollment was 7.0 (5.0) years

Table 1. Baseline Demographics and Disease Characteristics

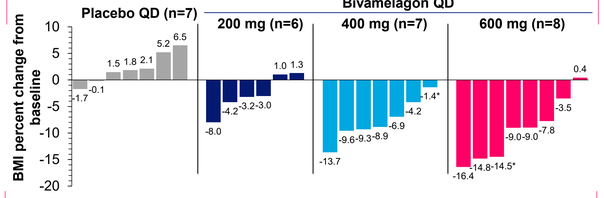
	Placebo (n=7)	Bivamelagon QD 200 mg (n=6)	Bivamelagon QD 400 mg (n=7)	Bivamelagon QD 600 mg (n=8)
Age, mean (SD), y	27.0 (20.2)	20.2 (9.2)	21.0 (8.0)	31.9 (23.0)
Sex, n (%)				
Male	4 (57.1)	3 (50.0)	3 (42.9)	5 (62.5)
Female	3 (42.9)	3 (50.0)	4 (57.1)	3 (37.5)
Race, n (%)				
White	6 (85.7)	6 (100.0)	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, kg	108.0 (42.3)	118.0 (35.6)	103.0 (29.3)	106.2 (22.4)
Waist circumference, cm	113.4 (20.3)	119.9 (14.4)	112.8 (22.7)	119.4 (20.9)
BMI, kg/m^2	37.0 (7.7)	38.0 (6.2)	37.7 (9.0)	41.4 (10.7)
Weekly score for "most hunger," n	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; QD, once daily; SD, standard deviation.

Participant Disposition

- In total, 27 of 28 participants completed the 14-week trial
  - One participant (bivamelagon 400 mg) discontinued because of a hematochezia serious adverse event at week 1
  - One participant receiving bivamelagon 600 mg was deemed to be nonadherent at different times during the trial on the basis of pill count and pharmacokinetic analysis (data not shown)
- Twenty-six of 28 participants entered the OLE
  - One participant had nausea and vomiting related to a period of adrenal insufficiency and chose not to continue into the OLE

Figure 2. Individual Percentage Changes in BMI From Baseline to Week 14*

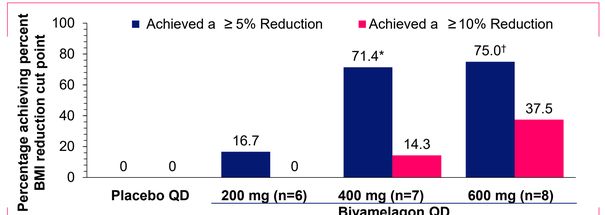


*Last observation carried forward (1 participant receiving bivamelagon 400 mg discontinued treatment on Week 1 and 1 participant receiving bivamelagon 600 mg discontinued treatment on Week 10. BMI, body mass index; QD, once-daily).

Efficacy

- Larger individual participant body mass index (BMI) reductions were observed in the higher dose cohorts relative to placebo (Figure 2)
- The primary endpoint at Week 14 was met with all bivamelagon cohorts reaching statistically significant greater percent BMI reduction versus placebo
- Participants receiving placebo had an average percent BMI increase from baseline of +2.18%
- Dose-dependent BMI reductions were seen across the bivamelagon cohorts with −2.68% (P=0.0180) for 200 mg, −7.69% (P =0.0002) for 400 mg, and −9.31% (p=0.0004) for 600 mg
- Significantly more participants achieved ≥5% reduction in percent BMI at Week 14 in the 400-mg and 600-mg cohorts (Figure 3)

Figure 3. Participants Achieving Percent BMI Reduction Criteria at Week 14



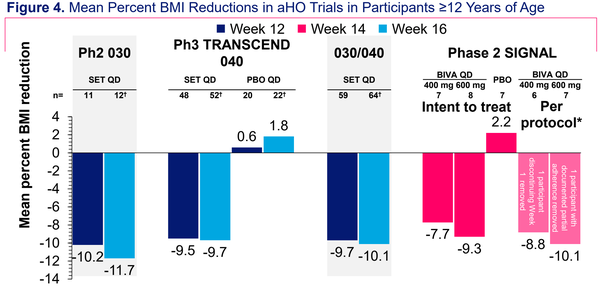
*P=0.0105, †P= 0.0056 versus placebo.

- Large pill size was reported to negatively affect adherence in some younger participants

BMI Reductions Following MC4R Agonist Treatment Across aHO Trials

- BMI reductions in the bivamelagon arm were comparable to those seen in setmelanotide aHO trials in participants ≥12 years of age at similar time points (Figure 4)

Figure 4. Mean Percent BMI Reductions in aHO Trials in Participants ≥12 Years of Age



*One participant in 400-mg cohort and 1 participant in 600-mg cohort were removed because of Week-1 discontinuation and documented partial adherence, respectively. †Last observation carried forward performed for Week 16 only. Participants receiving concomitant glucagon-like peptide 1 removed from setmelanotide trials to balance comparison. BIVA, bivamelagon; PBO, placebo; QD, once daily; SET, setmelanotide.

- Participants in the bivamelagon 400- and 600-mg cohorts achieved statistically significantly greater reductions in the weekly average of daily "most hunger" score at Week 14 (Figure 5)

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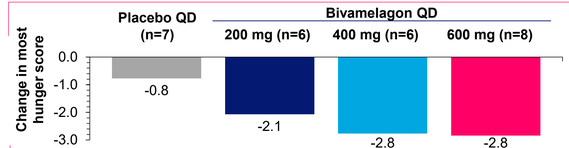
Figure 5. Mean Reduction in Most Hunger Score at Week 14



Weekly average of daily scores. One participant receiving 400 mg of bivamelagon who did not complete the trial did not have a Week-14 score and was not included.

Safety

- One participant in the 400-mg cohort discontinued treatment after the first few doses because of a serious adverse event of hematochezia; the participant's history of hemorrhoids and diarrhea and concomitant use of prednisone may have contributed to the event
- Another participant did not progress into the OLE because of nausea and vomiting associated with adrenal insufficiency
- The adverse event profile was generally consistent with that previously observed in setmelanotide trials, and no clear dose-dependent trends were observed (Table 2)

Table 2. Safety Summary

	Placebo (n=7)	Bivamelagon QD 200 mg (n=6)	Bivamelagon QD 400 mg (n=7)	Bivamelagon QD 600 mg (n=8)	Bivamelagon QD All BIVA (n=21)
AE category, n (%)					
Any AE	6 (85.7)	6 (100.0)	7 (100.0)	8 (100.0)	21 (100.0)
Serious AEs	1 (14.3)	0	1 (14.3)	0	1 (4.8)
Treatment-related AEs	3 (42.9)	6 (100.0)	7 (100.0)	8 (100.0)	21 (100.0)
Treatment-related serious AEs	0	0	1 (14.3)	0	1 (4.8)
Grade ≥3 AE	1 (14.3)	0	2 (28.6)	0	2 (9.5)
AEs leading to study drug discontinuation*	0	0	1 (14.3)	0	1 (4.8)
Most common (≥10% in all BIVA), n (%)					
Nausea	2 (28.6)	6 (100.0)	5 (71.4)	4 (50.0)	15 (71.4)
Diarrhea	1 (14.3)	2 (33.3)	5 (71.4)	3 (37.5)	10 (47.6)
Vomiting	2 (28.6)	2 (33.3)	4 (57.1)	4 (50.0)	10 (47.6)
Headache	2 (28.6)	1 (16.7)	5 (71.4)	0	6 (28.6)
Abdominal pain	0	1 (16.7)	2 (28.6)	1 (12.5)	4 (19.0)
Fatigue	0	1 (16.7)	2 (28.6)	1 (12.5)	4 (19.0)
Nasopharyngitis	1 (14.3)	1 (16.7)	2 (28.6)	0	3 (14.3)
Depression rating scale score increase	0	1 (16.7)	1 (14.3)	1 (12.5)	3 (14.3)
Decreased appetite	0	1 (16.7)	2 (28.6)	0	3 (14.3)
AEs of special interest, n (%)	0	2 (33.3)	3 (42.9)	0	5 (23.8)
Skin pigmentation†	0	2 (33.3)	2 (28.6)	0	4 (19.0)
Adrenal AEs	0	0	1 (14.3)	0	1 (4.8)

*Rectal bleeding. †One placebo-treated participant had skin hyperpigmentation that was considered not treatment related and not included by the Investigator as an AE of special interest. AE, adverse event; BIVA, bivamelagon; QD, once daily.

Conclusions

- In this Phase 2 trial, bivamelagon was associated with statistically significant and clinically meaningful weight reductions after only 14 weeks of treatment
- BMI reductions following bivamelagon were comparable to reductions seen in setmelanotide aHO trials
- Overall, bivamelagon demonstrated a safety profile consistent with its MC4R agonism and similar to that observed with setmelanotide
  - In contrast to setmelanotide, hyperpigmentation with bivamelagon was rare (4 cases) and limited to small, localized areas
- Twenty-six participants continued on to receive bivamelagon treatment in an OLE
- The large pill size influenced adherence in some younger participants; a smaller tablet is currently in development
- A Phase 3 trial with bivamelagon in participants with aHO is planned to commence in 2026

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