Poster 3.265

A First in Human Phase 1 Study Evaluating the Safety and Tolerability of BHV-7000, a Novel, Selective Kv7.2/7.3 Potassium Channel Activator, in Healthy Adults

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CONCLUSIONS

1. BHV-7000 was safe and well-tolerated at single doses up to 100 mg and multiple doses up to 120 mg daily for 15 days
2. Adverse events (AEs) typically associated with other anti-seizure medications (ASMs), such as somnolence and cognitive/mood disturbances, were not reported, which represents a potential paradigm shift in epilepsy treatment
3. These findings support the continued clinical development of BHV-7000 in epilepsy

INTRODUCTION

- Approximately one-third of people with epilepsy are refractory to treatment, despite the availability of ASMs, surgery, and dietary therapy[1-4]
- AEs associated with ASMs, such as somnolence and cognitive/mood disturbances, can impact quality of life and treatment adherence[5]
- BHV-7000 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels,[6,7] a clinically validated target in epilepsy[8]
- In preclinical studies, BHV-7000 showed minimal gamma-aminobutyric acid type A ($GABA_A$) receptor activation and exhibited potent anti-seizure efficacy in the maximal electroshock seizure model without negatively impacting neurobehavior or motor function (see AES 2023 poster 2.249)[6,7]
- The pharmacodynamic activity of BHV-7000 in the brain of healthy adults was demonstrated in a phase 1 study by dose-dependent increases in electroencephalograph spectral power (see AES 2023 poster 2.510)[9]

References: 1. Löscher W, et al. *Pharamcol Rev*. 2020;72(3):606-638. **2.** Laxer KD, et al. *Epilepsy Behav*. 2014;37:59-70. **3.** Guerrini R, et al. *Neurology*. 2021;97(17):817-831. **4.** Kwan P, et al. *J Neurol Neurosurg Psychiatry*. 2004;75(10):1376-1381. **5.** Eatock J, et al. *Neuropsychiatr Dis Treat*. 2007;3(1):117-131. **6.** Dworetzky S, et al. Presented at ILAE. Sep 2-6, 2023; Dublin, Ireland. Poster P015. **7.** Picchione K, et al. Presented at AES. Dec 1-5, 2023; Orlando, FL. Poster 2.249. **8.** Köhling R, et al. *Cold Spring Harb Perspect Med*. 2016;6(5):a022871. **9.** Lerner J, et al. Presented at AES. Dec 1-5, 2023; Orlando, FL. Poster 2.510.

Disclosures: BA, JL, EA, HS, MB, SD, LD, RK, and IQ are employed by and hold stock/stock options in Biohaven Pharmaceuticals. BF is employed by Syneos Health.

Acknowledgments: This study was funded by Biohaven Pharmaceuticals. Medical writing and editorial support were provided by James Banigan, PhD, and Shannon Davis of Apollo Medical Communications, part of Helios Global Group, and funded by Biohaven Pharmaceuticals.

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American Epilepsy Society (AES) Annual Meeting • December 1-5, 2023 • Orlando, Florida & Virtual

OBJECTIVE and METHODS

Objective

- Evaluate the safety and tolerability of single- and multiple-ascending doses (SAD and MAD) of oral BHV-7000 in healthy subjects

Methods

- A first-in-human, phase 1, single-center, double-blind, placebo-controlled, sequential SAD/MAD study in healthy adults was conducted
- SAD subjects were randomized 3:1 to BHV-7000 (4, 10, 25, 50, or 100 mg) or placebo under fasting conditions
  - Subjects in the 25-mg SAD cohort received study drug under both fasting and fed conditions
- MAD subjects were randomized 3:1 to BHV-7000 (10, 25, or 40 mg daily) or placebo and dosed for 15 days
- Key inclusion criteria
  - Healthy male or nonchildbearing female subjects ≥18 and ≤55 years of age
  - Body mass index (BMI) >18.0 and <30.0 kg/m^2
  - Body weight ≥55.0 kg
- Safety evaluations included AE monitoring, clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, and Sheehan Suicidality Tracking Scale (S-STS) score
- A safety review committee assessed the safety and tolerability after completion of each dose level prior to dose escalation

RESULTS

Disposition

- In the SAD and MAD cohorts, 61 subjects received BHV-7000 (n = 46) or placebo (n = 15)
  - The SAD cohort included 39 subjects randomized to BHV-7000 or placebo
  - The MAD cohort included 22 subjects randomized to BHV-7000 or placebo

Demographics

- Demographics and baseline characteristics are presented in **Table 1**
- Mean age in the SAD and MAD cohorts was 40.1 and 40.0 years, respectively
- The majority of subjects were male (SAD, 87%; MAD, 91%) and white (SAD, 95%; MAD, 91%)

Safety and Tolerability

- In the SAD cohort, the most common treatment-emergent AEs (TEAEs) were headache and abdominal discomfort (**Table 2**)
- In the MAD cohort, the most common TEAEs were headache and back pain (**Table 3**)
- Across the dosing groups in the SAD and MAD cohorts, there were low rates of nervous system TEAEs (**Table 4**). No cases of somnolence were reported
- There were no serious TEAEs, severe TEAEs, nor deaths reported in this study
- The majority of TEAEs were mild in severity and resolved by the conclusion of the study
- There were no clinically meaningful trends in laboratory values, nor were there clinically meaningful trends or treatment-related findings identified for vital signs, ECGs, or S-STS

Table 1. Subject Demographics and Characteristics

Characteristic		Single-Ascending Dose n = 39	Multiple-Ascending Dose n = 22
Mean (SD) age, years		40.1 (9.7)	40.0 (9.6)
Sex, n (%)	Female	5 (12.8)	2 (9.1)
	Male	34 (87.2)	20 (90.9)
Race, n (%)	Asian	0	1 (4.5)
	Black	2 (5.1)	1 (4.5)
	White	37 (94.9)	20 (90.9)
Mean (SD) BMI, kg/m^2		25.4 (2.5)	25.4 (2.6)

SD, standard deviation.

Table 2. TEAEs Occurring in ≥2 Subjects Receiving BHV-7000 in the SAD Cohorts

	BHV-7000							
AE, n (%)	4 mg n = 6	10 mg n = 6	25 mg (Fasted) n = 6	25 mg (Fed) n = 6	50 mg n = 6	100 mg n = 5	BHV-7000 Overall n = 29	Placebo n = 10
Headache	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0	3 (10.3)	0
Abdominal discomfort	0	1 (16.7)	0	1 (16.7)	0	0	2 (6.9)	0

All AEs reported in the SAD cohorts were mild in severity and resolved.

Table 3. TEAEs Occurring in ≥2 Subjects Receiving BHV-7000 in the MAD Cohorts

	BHV-7000						
AE, n (%)	10 mg n = 5	25 mg n = 6	40 mg n = 6	80 mg[a] n = 6	120 mg[a] n = 6	BHV-7000 Overall[b] n = 29	Placebo[b] n = 9
Headache	0	0	3 (50.0)	1 (16.7)	2 (33.3)	6 (20.7)	3 (33.3)
Back pain	1 (20.0)	0	2 (33.3)	2 (33.3)	1 (16.7)	6 (20.7)	0
Constipation	0	0	1 (16.7)	1 (16.7)	1 (16.7)	3 (10.3)	3 (33.3)
Dizziness	0	0	0	2 (33.3)	1 (16.7)	3 (10.3)	2 (22.2)
Abdominal pain	0	0	0	2 (33.3)	0	2 (6.9)	1 (11.1)
Fatigue	0	0	0	1 (16.7)	1 (16.7)	2 (6.9)	2 (22.2)

All AEs reported in the MAD cohorts were mild in severity, except 1 case of back pain (moderate severity, 40 mg) and 1 case of dizziness (moderate severity, 80 mg), and resolved.
[a]Data are included from a separate study evaluating higher MAD doses.
[b]Data are pooled across studies.

Table 4. Nervous System TEAEs Occurring in ≥1 Subject Receiving BHV-7000

Single-Ascending Dose

	BHV-7000							
Nervous System AE,[a] n (%)	4 mg n = 6	10 mg n = 6	25 mg (Fasted) n = 6	25 mg (Fed) n = 6	50 mg n = 6	100 mg n = 5	BHV-7000 Overall n = 29	Placebo n = 10
Headache	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0	3 (10.3)	0
Dizziness	0	1 (16.7)	0	0	0	0	1 (3.4)	0
Myoclonus	0	0	1 (16.7)	0	0	0	1 (3.4)	0

Multiple-Ascending Dose

	BHV-7000						
Nervous System AE,[a] n (%)	10 mg n = 5	25 mg n = 6	40 mg n = 6	80 mg[b] n = 6	120 mg[b] n = 6	BHV-7000 Overall[c] n = 29	Placebo[c] n = 9
Headache	0	0	3 (50.0)	1 (16.7)	2 (33.3)	6 (20.7)	3 (33.3)
Dizziness	0	0	0	2 (33.3)	1 (16.7)	3 (10.3)	2 (22.2)
Hypoesthesia	0	0	0	0	1 (16.7)	1 (3.4)	0
Paresthesia	0	0	0	0	1 (16.7)	1 (3.4)	0

All nervous system AEs reported in the SAD and MAD cohorts were mild in severity, except 1 case of dizziness (moderate severity, 80 mg), and resolved.
[a]TEAEs within the system organ class of nervous system disorders.
[b]Data are included from a separate study evaluating higher MAD doses.
[c]Data are pooled across studies.