Poster 007

# 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[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[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.

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## 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

- Phase 1, double-blind, placebo-controlled, sequential SAD/MAD studies in healthy adults were 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, 40, 80, or 120 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, 77 subjects received BHV-7000 (n = 58) or placebo (n = 19)
  - The SAD cohort included 39 subjects randomized to BHV-7000 or placebo
  - The MAD cohort included 38 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 40.3 years, respectively
- The majority of subjects were male (SAD, 87%; MAD, 95%) and white (SAD, 95%; MAD, 90%)

### 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 = 38 |
|---|---|---|---|
| Mean (SD) age, years | | 40.1 (9.7) | 40.3 (9.1) |
| Sex, n (%) | Female | 5 (12.8) | 2 (5.3) |
| | Male | 34 (87.2) | 36 (94.7) |
| Race, n (%) | Asian | 0 | 2 (5.3) |
| | Black | 2 (5.1) | 2 (5.3) |
| | White | 37 (94.9) | 34 (89.5) |
| Mean (SD) BMI, kg/m$^2$ | | 25.4 (2.5) | 25.8 (2.5) |

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.

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