

Phase 1 Multiple-Ascending Dose Studies Demonstrate Favorable Safety and Tolerability of BHV-7000, a Novel Kv7 Potassium Channel Activator

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INTRODUCTION

- Approximately one-third of people with epilepsy are refractory to treatment, despite the availability of antiseizure medications (ASMs), surgery, and dietary therapy¹⁻⁴
- Adverse events (AEs) associated with ASMs, such as somnolence and cognitive/mood disturbances, can impact quality of life and treatment adherence⁵
- BHV-7000 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels in late-stage clinical development for epilepsy and neuropsychiatric disorders⁶⁻¹⁰
- Compared with ezogabine and its analogs, BHV-7000 belongs to a significantly different structural class and was rationally designed to differentiate on key properties¹¹
- In preclinical studies, BHV-7000 showed minimal gamma-aminobutyric acid type A (GABAA) receptor activation and exhibited potent antiseizure efficacy in the maximal electroshock seizure model without negatively impacting neurobehavior or motor function^{6,7}
- In a prior first-in-human single-ascending dose study in healthy adults, BHV-7000 was safe and well tolerated at doses up to 100 mg¹²
- 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 power¹³

OBJECTIVE

- Assess the safety and tolerability of BHV-7000 across multiple-ascending dose (MAD) studies completed to date

METHODS

- Results were pooled from phase 1 placebo-controlled MAD studies
- MAD participants were randomized to oral BHV-7000 immediate release (10, 25, 40, 80, or 120 mg daily), extended release (25, 50, or 75 mg daily), or matching placebo and dosed for up to 15 days
- Key inclusion criteria
 - Healthy male or nonchildbearing female participants aged ≥ 18 and ≤ 55 years
 - Body mass index ≥ 18.0 and ≤ 30.0 kg/m²
 - Body weight ≥ 55.0 kg
- Safety evaluations included AE monitoring, clinical laboratory tests, vital signs, electrocardiograms, physical examinations, and suicidality assessments
- A safety review committee assessed the safety and tolerability after completion of each dose level prior to dose escalation

RESULTS

Disposition

- Across the MAD cohorts, 66 participants received BHV-7000 (n = 53) or placebo (n = 13)

Demographics

- Demographics and baseline characteristics are presented in **Table 1**
- Mean age was 39.0 years, and the majority of participants were male (89.4%) and White (83.3%)

Safety and Tolerability

- There were no deaths, serious AEs, severe AEs, or dose-limiting toxicities
- In the MAD cohort, the most common treatment-emergent AEs were headache (11.3%) and back pain (11.3%) (**Table 2**)
 - No AEs were reported among participants receiving BHV-7000 75 mg extended release (n = 12), the highest dose utilized in ongoing phase 2/3 studies
- There were low rates of central nervous system-related AEs (**Table 3**); no somnolence was reported
- The majority of AEs were mild and resolved spontaneously

Table 1. Participant Demographics and Characteristics

| Characteristic | | Multiple-Ascending Dose N = 66 |
|-----------------------------------|--------|-----------------------------------|
| Mean age, years | | 39.0 |
| Sex, n (%) | Female | 7 (10.6) |
| | Male | 59 (89.4) |
| Race, n (%) | Asian | 2 (3.0) |
| | Black | 9 (13.6) |
| | White | 55 (83.3) |
| Mean BMI, kg/m² | | 25.9 |

BMI, body mass index.

Table 2. TEAEs Occurring in $\geq 5\%$ of Participants Receiving BHV-7000

| AE, n (%) | BHV-7000 | | | | | | | | BHV-7000 Overall n = 53 | Placebo n = 13 |
|---------------------|----------------|----------------|----------------|----------------|-----------------|-------------------|-------------------|--------------------|----------------------------|-------------------|
| | 10 mg n = 5 | 25 mg n = 6 | 40 mg n = 6 | 80 mg n = 6 | 120 mg n = 6 | 25 mg ER n = 6 | 50 mg ER n = 6 | 75 mg ER n = 12 | | |
| Headache | 0 | 0 | 3 (50.0) | 1 (16.7) | 2 (33.3) | 0 | 0 | 0 | 6 (11.3) | 3 (23.1) |
| Back pain | 1 (20.0) | 0 | 2 (33.3) | 2 (33.3) | 1 (16.7) | 0 | 0 | 0 | 6 (11.3) | 0 |
| Constipation | 0 | 0 | 1 (16.7) | 1 (16.7) | 1 (16.7) | 0 | 0 | 0 | 3 (5.7) | 3 (23.1) |
| Dizziness | 0 | 0 | 0 | 2 (33.3) | 1 (16.7) | 0 | 0 | 0 | 3 (5.7) | 2 (15.4) |

All AEs 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. AE, adverse event; ER, extended release; TEAE, treatment-emergent adverse event.

Table 3. Nervous System TEAEs Occurring in ≥ 1 Participant Receiving BHV-7000

| AE, n (%) | BHV-7000 | | | | | | | | BHV-7000 Overall n = 53 | Placebo n = 13 |
|---------------------|----------------|----------------|----------------|----------------|-----------------|-------------------|-------------------|--------------------|----------------------------|-------------------|
| | 10 mg n = 5 | 25 mg n = 6 | 40 mg n = 6 | 80 mg n = 6 | 120 mg n = 6 | 25 mg ER n = 6 | 50 mg ER n = 6 | 75 mg ER n = 12 | | |
| Headache | 0 | 0 | 3 (50.0) | 1 (16.7) | 2 (33.3) | 0 | 0 | 0 | 6 (11.3) | 3 (23.1) |
| Dizziness | 0 | 0 | 0 | 2 (33.3) | 1 (16.7) | 0 | 0 | 0 | 3 (5.7) | 2 (15.4) |
| Dysgeusia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (1.9) | 0 |
| Hypoesthesia | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (1.9) | 0 |
| Paresthesia | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (1.9) | 0 |
| Presyncope | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (1.9) | 0 |

All nervous system AEs were mild in severity, except 1 case of dizziness (moderate severity, 80 mg), and resolved. AE, adverse event; ER, extended release; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- BHV-7000 was safe and well tolerated in phase 1 MAD studies up to 120 mg daily (immediate release) or 75 mg daily (extended release) for up to 15 days
- AEs typically associated with other ASMs, such as somnolence and cognitive/mood disturbances, were not reported, which represents a potential paradigm shift in the treatment of epilepsy and other neuropsychiatric disorders
- Late-stage phase 2/3 studies are ongoing in epilepsy, major depressive disorder, and bipolar disorder; for more information visit biohavenclinicaltrials.com

DISCLOSURES: BA, JL, EA, HS, MB, SD, CJ, RK, AI, IQ, and VC are employed by and hold stock/stock options in Biohaven Pharmaceuticals.

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