POSTER
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Phase 1 Multiple-Ascending Dose Studies Demonstrate Favorable Safety and Tolerability of BHV-7000, a Novel Kv7 Kv7 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 therapy[1-4]
- Adverse events (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 in late-stage clinical development for epilepsy and neuropsychiatric disorders[6-10]
- Compared with ezogabine and its analogs, BHV-7000 belongs to a significantly different structural class and was rationally designed to differentiate on key properties[11]
- 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 mg[12]
- 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[13]

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/m^2
  - 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/m^2		25.9

BMI, body mass index.

Table 2. TEAEs Occurring in ≥ 5% of Participants Receiving BHV-7000

AE, n (%)	BHV-7000									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	BHV-7000 Overall n = 53	
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									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	BHV-7000 Overall n = 53	
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 and major depressive disorder; for more information visit biohavenclinicaltrials.com

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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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