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Safety and Tolerability of BHV-7000, a Novel Kv7 Potassium Channel Activator: Results From Phase 1 Single- and Multiple-Ascending Dose Studies

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INTRODUCTION

- Approximately one-third of people with epilepsy are refractory to treatment, despite the availability of anti-seizure 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,[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]

OBJECTIVE

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

METHODS

- Phase 1, double-blind, placebo-controlled, sequential SAD/MAD studies in healthy adults were conducted
- SAD participants were randomized 3:1 to BHV-7000 (4, 10, 25, 50, or 100 mg) or placebo under fasting conditions
  - Participants in the 25-mg SAD cohort received study drug under both fasting and fed conditions
- MAD participants 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 males or nonchildbearing females ≥ 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 participants received BHV-7000 (n = 58) or placebo (n = 19)
  - The SAD cohort included 39 participants randomized to BHV-7000 or placebo
  - The MAD cohort included 38 participants 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 participants were male (SAD, 87%; MAD, 95%) and White (SAD, 95%; MAD, 90%)

Table 1. Participant 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 Participants 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.

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 3. TEAEs Occurring in ≥ 2 Participants 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 Participant 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.

CONCLUSIONS

- 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
- AEs typically associated with other ASMs, such as somnolence and cognitive/mood disturbances, were not reported, which represents a potential paradigm shift in epilepsy treatment
- These findings support the continued clinical development of BHV-7000 in epilepsy

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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.

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