POSTER
P189

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

Bharat Awsare, MD; Jason Lerner, MD; Eric Ashbrenner, MS; Heather Sevinsky, MS; Steven Dworetzky, PhD; Christopher Jensen, PharmD; Randall Killingsworth, BA; Andrea Ivans, MHS; Irfan Qureshi, MD; Vladimir Coric, MD; Michael Bozik, MD

Biohaven Pharmaceuticals, New Haven, CT

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]
- Opakalim (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, opakalim belongs to a significantly different structural class and was rationally designed to differentiate on key properties[11]
- In preclinical studies, opakalim showed minimal gamma-aminobutyric acid type A ($GABA_A$) 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, opakalim was safe and well tolerated at doses up to 100 mg[12]
- The pharmacodynamic activity of opakalim 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 opakalim 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 opakalim 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 opakalim (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 opakalim 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 2. TEAEs Occurring in ≥ 5% of Participants Receiving Opakalim

	Opakalim									
AE, n (%)	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	Opakalim Overall n = 53	Placebo n = 13
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 Opakalim

	Opakalim									
AE, n (%)	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	Opakalim Overall n = 53	Placebo n = 13
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.

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.

CONCLUSIONS

- Opakalim (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

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

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

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.** Suarez V, et al. Presented at: Eilat International Educational Course; Sep 15-20, 2024; Limassol, Cyprus. **9.** NIH. Accessed Nov 12, 2024. https://clinicaltrials.gov/study/NCT06419608. **10.** NIH. Accessed Nov 12, 2024. https://clinicaltrials.gov/study/NCT06419582. **11.** Terman SW, et al. *Epilepsia.* 2024;65(4):833-845. **12.** Awsare B, et al. Presented at: AES; Dec 1-5, 2023; Orlando, FL. Poster 3.265. **13.** Lerner J, et al. Presented at: AES; Dec 1-5, 2023; Orlando, FL. Poster **2.510.**

To download a copy of this poster, scan QR code.