Discovery and Characterization of BHV-7000: A Novel Kv7.2/7.3 Activator for the Treatment of Epilepsy

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CONCLUSIONS

1. BHV-7000 is a novel and differentiated activator of Kv7.2/7.3 channels
2. BHV-7000 is chemically and pharmacologically distinct from ezogabine
3. BHV-7000 "dials-out" $GABA_A$ receptor activation
4. BHV-7000 is potent in the MES epilepsy model without impact on neurobehavior
5. BHV-7000 was well-tolerated in Phase 1 SAD/MAD studies without CNS adverse effects typical of anti-seizure medications

Disclosures: SD, KP, LR, and MB are employed by and hold stock/stock options in Biohaven Pharmaceuticals.

References: 1. Cooper EC. *Semin Cell Dev Biol*. 2011; 22:185-192; **2.** Vigil FA. *Front Physiol*. 2020;11:688.

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INTRODUCTION

- The Kv7 (KCNQ) subfamily of voltage-gated potassium channels consists of 5 members (Kv7.1-5) that have various roles involving currents in the heart, nerve, brain, and epithelia[1]
- Kv7.2/7.3 channels are low-threshold voltage-gated potassium channels expressed in the central nervous system (CNS) that modulate neuronal excitability[2]
- Mutations in Kv7.2/7.3 channels can lead to seizures or other epileptic syndromes
- Preclinical studies have shown that activating Kv7.2/7.3 hyperpolarizes resting membrane potential (RMP), increases action potential (AP) threshold, and has potent anti-seizure effects
- Precision targeting of Kv7 potassium channels may deliver robust efficacy while minimizing the risk of adverse effects associated with traditional anti-epileptic drugs
- Although the Kv7.2/7.3 channel is a validated target for treating seizures, modulators with improved potency, selectivity, and tolerability are needed
- BHV-7000 is a novel and differentiated activator of heteromeric Kv7.2/7.3 potassium channels in development for the treatment of epilepsy

OBJECTIVE

- The objective of this study was to describe the discovery and characterization of BHV-7000

METHODS OVERVIEW

- A screening tier was designed to discover potent and selective Kv7.2/7.3 activators
- Fluorescent and electrophysiological assays were employed to characterize lead compounds
- Antiseizure efficacy was evaluated in rats in the maximal electroshock seizure (MES) model and tolerability was assessed by neurological score (NS)
- Standard ADME and toxicology assays were used
- A first-in-human phase 1 single ascending dose/multiple ascending dose (SAD/MAD) study assessed safety, tolerability, and pharmacokinetics in healthy volunteers

METHODS AND RESULTS

Effects of BHV-7000 on $V_{1/2}$

- hKv7.2/7.3 channels stably expressed in U2-OS cells were used and examined on the QPatch48 Automated Patch Clamp system
- Three concentrations (0.3 µM, 1 µM, and 3 µM) of BHV-7000 were each applied to a minimum of 4 separate cells
- Peak inward tail current amplitude recorded at -120 mV was measured for each sweep
- Data were normalized relative to the largest inward tail current measured for each cell (I/Imax)
- Mean (SD) data were fitted with a Boltzmann equation to produce the half-maximal activation voltage ($V_{1/2}$)
- The bottom of the curves were fixed to zero
- At 3 µM, BHV-7000 shifted the half-maximal activation potential by -20.97 mV (**Figure 1** and **Table 1**)

Figure 1. Voltage Dependence of Activation

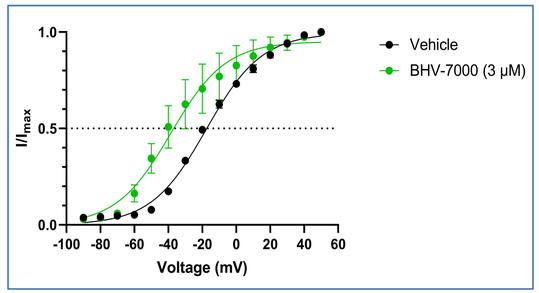


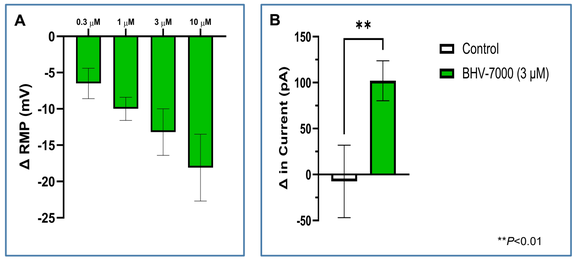
Table 1. Voltage Dependence of Activation

	0.3 µM	1.0 µM	3.0 µM
$V_{1/2}$ shift	-7.60	-15.21	-20.97

Effects of BHV-7000 on RMP and AP Threshold

- Whole-cell current clamp recordings were performed on culture days 7-9 from rat cortical neurons (Transnetyx)
- BHV-7000 produced a concentration-dependent hyperpolarization of the RMP (**Figure 2A**)
- Manual patch clamp recordings from rat cortical neurons (Lonza) were used to determine effects of BHV-7000 on action potential threshold
- The change in AP threshold at 3 µM was significantly higher for BHV-7000 (n=5) than control (n=4) (p=0.0058, unpaired t-test with Welch's correction) (**Figure 2B**)

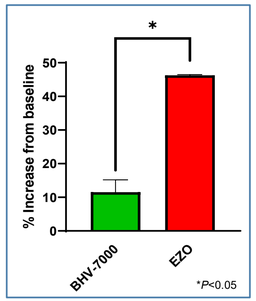
Figure 2. Hyperpolarization of RMP and Change in the AP Threshold



$GABA_A$ α1β3γ2 Receptor Activation

- The EC_{10} concentration of GABA (0.85 µM) was added to establish a baseline response
- Then 10 µM ezogabine (n=2) or BHV-7000 (n=2) was applied in the presence of GABA for 2 seconds
- BHV-7000 and ezogabine produced respective potentiation of 12% and 46% (**Figure 3**)
- The $GABA_A$ potentiation of BHV-7000 was significantly lower than ezogabine (p=0.0469, unpaired t-test with Welch's correction)

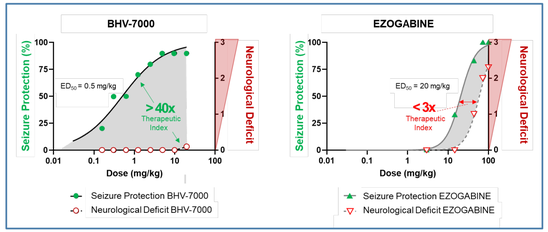
Figure 3. Change From Baseline in $GABA_A$ Response



BHV-7000 In Vivo Efficacy and Neurobehavior Effects

- Efficacy and neurological deficit were assessed in the rat MES model
- Data for BHV-7000 (n=10/group) and ezogabine (n=6/group) were collected in independent experiments conducted by InterVivo Solutions
- MES testing was performed at the approximate C_{max} for BHV-7000 (1 h after oral dosing) and for ezogabine (30 min after oral dosing)
- Neurological deficit testing was conducted 5 minutes prior to the MES test and was used to calculate the therapeutic index

Figure 4. Efficacy and Neurological Deficit in Rat MES



BHV-7000 Phase 1 Safety and Tolerability

- In a Phase I SAD/MAD clinical trial of BHV-7000, single doses (up to 100 mg) and multiple doses (up to 40 mg) daily for 15 days were well-tolerated
- CNS-related adverse events typical of anti-seizure medications were not reported (**Table 2**)
- Most adverse events were mild and resolved spontaneously; no serious or severe adverse events or dose-limiting toxicities were reported

Table 2. CNS Adverse Events[a] in the MAD Pooled Population

	BHV-7000 MAD pooled (n=17)
Somnolence	0%
Headache	18%
Balance disorder	0%
Dizziness	0%
Memory impairment	0%
Sensory disturbance	0%
Speech disorder	0%

[a]MedDRA Preferred Term within the System Organ Class of nervous system disorders.
MAD=multiple ascending dose