Poster 2.249

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

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CONCLUSIONS

1. BHV-7000 is a potent activator of Kv7.2/7.3 channels, impacting both deactivation kinetics and voltage dependence of activation
2. BHV-7000 requires Kv7.2 W236 residue for channel activity
3. No significant activation of the α1β3γ2 gamma-aminobutyric acid type A ($GABA_A$) receptor
4. BHV-7000 is potent in the maximal electroshock seizure (MES) test without impact on neurobehavior or motor behavior

INTRODUCTION

- Kv7.2/7.3 channels are voltage-gated potassium channels expressed throughout the central nervous system (CNS) that modulate neuronal excitability
- 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 in development for the treatment of epilepsy, KCNQ2-associated developmental and epileptic encephalopathies (KCNQ2-DEE), and neuropsychiatric disorders
- BHV-7000 was well-tolerated in a first-in-human, phase 1, single- and multiple-ascending dose study (see AES 2023 poster 3.265)
- Pharmacodynamic activity of BHV-7000 in the brain was demonstrated in a phase 1 study by dose-dependent increases in electroencephalograph spectral power (see AES 2023 late-breaking poster 2.510)

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

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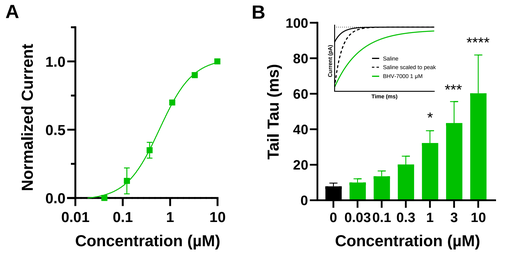
IN VITRO METHODS/RESULTS

Potent Activator of Kv7.2/7.3

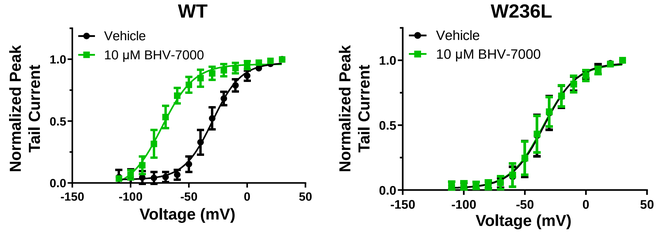
- Whole-cell voltage-clamp experiments were performed on the Sophion Bioscience QPatch®. Steady-state currents were measured at -30 mV, followed by a deactivating pulse at -100 mV
- **(A)** BHV-7000 is a potent activator of Kv7.2/7.3 channels, with a half maximal effective concentration (EC_{50}) of 0.6 μM
- **(B)** BHV-7000 produced a concentration-dependent change in deactivation kinetics (tail tau) and significantly slowed deactivation kinetics at 1 μM and above (one-way analysis of variance, Dunnett's test = 0.0115)



Inset is representative trace at 1 μM.

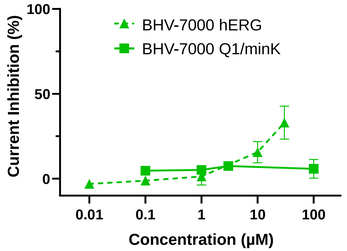
BHV-7000 Requires W236 for Activity

- W236 mutation studies on Kv7.2 were conducted in transiently transfected human embryonic kidney (HEK) cells by ChemPartner. Peak tail currents were measured at 0 mV after activating pulses from -110 to +30 mV
- BHV-7000 shifts the voltage dependence of activation of wild-type (WT) Kv7.2 channels -45 mV ± 4.4 at 10 μM
- All activity is lost in the presence of the W236L mutation



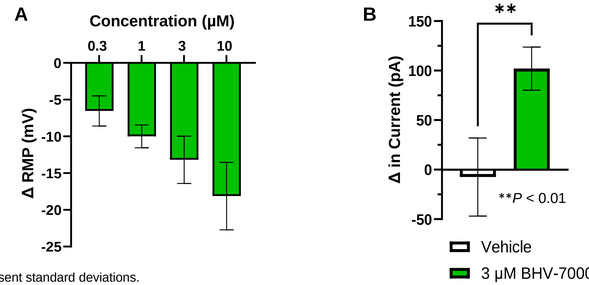
No Significant Activity Against hERG and Q1/minK

- HEK hERG- and Q1/minK-expressing cells were examined by manual-patch electrophysiology at Eurofins
- Inhibitory concentrations (IC_{20}) were not reported due to less than 50% inhibition at the top concentration (30 μM)
- hERG results were confirmed in a Good Laboratory Practice hERG study



Effects on RMP and AP Threshold

- Current clamp recordings were performed to assess resting membrane potential (RMP) and action potential (AP) threshold using rat primary cortical neurons
- **(A)** In primary rat cortical neurons, BHV-7000 produced a concentration-dependent hyperpolarization of the RMP
- **(B)** BHV-7000 also significantly increased the AP threshold (P = 0.0058, unpaired t test with Welch's correction)

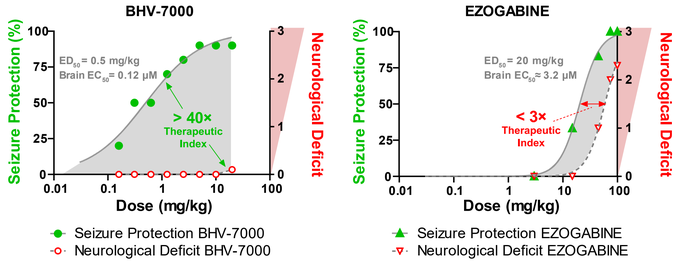


All error bars represent standard deviations.

IN VIVO METHODS/RESULTS

In Vivo Efficacy and No Neurobehavior Effects

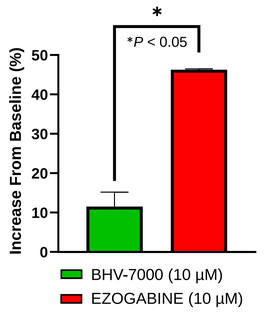
- Protection against seizures was assessed in the MES test using male Sprague Dawley rats. Data for BHV-7000 (n = 10/group) and ezogabine (n = 6/group) were collected in independent experiments conducted by InterVivo Solutions
- Neurological deficit testing was conducted 5 minutes prior to the MES test and was used to calculate the therapeutic index. This is a visual observation assessing changes in activity, ataxia, and body posture on a scale of 0-3



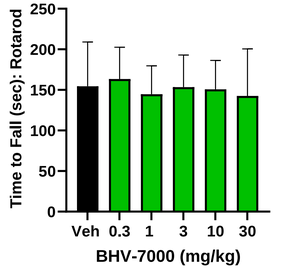
- BHV-7000 protects against MES-induced seizures, with a median effective dose (ED_{50}) of 0.5 mg/kg, while having no impact on neurobehavior and producing a therapeutic index > 40×
- Ezogabine has an ED_{50} of 20 mg/kg and impacts neurobehavior at similar doses required for efficacy, producing a therapeutic index < 3×

Off-Target and Additional Tolerability Measures

- $GABA_A$ receptor positive allosteric modulator (PAM) recordings were performed against the human α1β3γ2 receptor
- The $GABA_A$ receptor PAM potentiation of BHV-7000 was significantly lower than ezogabine (P = 0.0469, unpaired t test with Welch's correction)



- Motor impairment was assessed on the rotarod. Animals were placed on the rotarod, and an accelerating speed was applied from 4 to 40 rpm over 5 minutes; the time to fall was recorded
- There was no significant change in rotarod performance up to 30 mg/kg



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