**INTRODUCTION AND METHODS**

**Introduction**
- Kv7.2/3 channels are low-threshold, voltage-gated potassium channels expressed in the CNS that modulate neuronal excitability.
- Mutations in Kv7.2/3 channels can lead to seizures or other epileptic syndromes, including benign neonatal facial convulsions (BNFC) and KCNQ2-associated developmental and epileptic encephalopathies (KCNQ2DEE).
- Although the Kv7.3 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 stiff neck syndrome and KCNQ2DEE.

**Methods Overview**
- Kv7.2/3 potency experiments were conducted in human embryonic kidney (HEK) cells. Whole-cell clamp experiments were performed on the Signalert® patchclamp system, and steady-state currents were measured at voltage steps from -150 mV to 0 mV in 10 mV increments.
- Concentration-inhibition curves were conducted in 0-50 mM GABA with the Boltzmann equation to calculate the EC50.
- W236R mutation studies on Kv7.2 were conducted in transiently transfected HEK cells with Chloroplates. Peak tail currents at 0 mV were measured after activating pulses (150 ms). Voltage clamp experiments were performed on the Signalert® patchclamp system using rat primary cortical neurons. Cortical neurons were obtained from Transnetyx for RMP studies and Lona for GABA-ergic and I-V threshold studies.
- Protection against seizures was assessed in the MES test using male Sprague-Dawley rats. Dosages for BHV-7000 (n = 10/group) and ezogabine (n = 5/group) were collected in independent experiments conducted by InterVivo Solutions.

**METHODS**

**Potent Activator of Kv7.2/3**

BHV-7000 is a potent activator of Kv7.2/3 channels with a half-maximal effective concentration (EC50) of 0.6 μM.

BHV-7000 shifts the voltage dependence of activation of Kv7.2/3 channels to -21 mV at 3 μM.

**Effects on RMP and AP Threshold**

- **(A)** In primary 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).

**In Vivo RESULTS**

**BHV-7000 Requires W236 for Activity**

BHV-7000 shifts the voltage dependence of activation of wild-type (WT) Kv7.2 channels.

All activity is lost in the presence of W236L mutation.

W236L is also required for ezogabine activity.

**In Vivo Efficacy and No Neurobehavior Effects**

- **BHV-7000 protects against MES-induced seizures with a median effective dose (ED50) of 0.5 mg/kg while having no impact on neurobehavior, producing a therapeutic index > 40.**
- **Ezogabine has an ED50 of 20 mg/kg and impacts neurobehavior at efficacious doses required for efficacy, producing a therapeutic index < 3.**

**Off-Target and Additional Tolerability Measures**

- The GABAA receptor PAM potentiation of BHV-7000 was significantly lower than ezogabine (P = 0.0469, unpaired t-test with Welch’s correction).
- There was no significant change in rotarod performance up to 30 mg/kg.

**CLINICAL RESULTS**

**First-in-Human SAD/MAD Phase 1 Study**

- **CNS-related adverse events (AEs) typical of anti-seizure medications were not reported.**
- **Most AEs were mild and resolved spontaneously; no serious or severe AEs or dose-limiting toxicities were reported.**

**CONCLUSIONS**

1. BHV-7000 is a structurally and pharmacologically differentiated activator of Kv7.2/3 channels.
2. BHV-7000 activity requires Kv2.7 W236 residue for activity.
3. BHV-7000 “data-out” gamma-aminobutyric acid type A (GABAergic) receptor activation.
4. BHV-7000 is potent in the maximal electroshock seizure (MES) test without impact on neuro or motor behavior.
5. BHV-7000 was well tolerated in phase 1 single ascending and multiple ascending dose (SAD/MAD) studies without central nervous system (CNS) adverse effects typical of anti-seizure medications.

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

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