Poster P015

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 structurally and pharmacologically differentiated activator of Kv7.2/7.3 channels
2. BHV-7000 activity requires Kv7.2 W236 residue for activity
3. BHV-7000 "dials-out" gamma-aminobutyric acid type A ($GABA_A$) 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, LR, and MB are employed by and hold stock/stock options in Biohaven Pharmaceuticals.

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INTRODUCTION AND METHODS

Introduction

- Kv7.2/7.3 channels are low-threshold, voltage-gated potassium channels expressed in the CNS that modulate neuronal excitability
- Mutations in Kv7.2/7.3 channels can lead to seizures or other epileptic syndromes, including benign neonatal fetal convulsions (BNFC) and KCNQ2-associated developmental and epileptic encephalopathies (KCNQ2DEE)
- 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 adult focal epilepsy and KCNQ2DEE

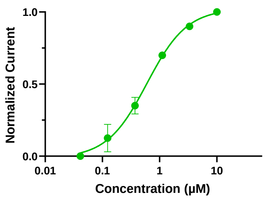
Methods Overview

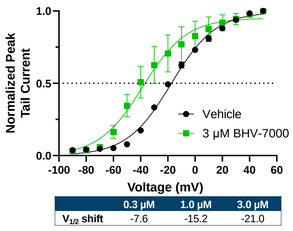
- Kv7.2/7.3 potency experiments were conducted in human embryonic kidney (HEK) cells. Whole-cell voltage-clamp experiments were performed on the Sophion Bioscience QPatch®, and steady-state currents were measured at -30 mV. Kv7.2/7.3 half maximal activation voltage ($V_{1/2}$) experiments were conducted in U2-OS cells by Metrion Biosciences. Peak inward tail currents were measured at -120 mV after activating pulses (-90 to +50 mV). Mean data were fit with a Boltzmann equation to calculate the $V_{1/2}$
- W236 mutation studies on Kv7.2 were conducted in transiently transfected HEK cells by ChemPartners. Peak tail currents at 0 mV were measured after activating pulses (-110 to +30 mV)
- Current clamp recordings were performed to assess resting membrane potential (RMP) and action potential (AP) threshold using rat primary cortical neurons. Cortical neurons were obtained from Transnetyx for RMP studies and Lonza for AP threshold studies
- 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
- A separate cohort of animals was tested for motor impairment on the rotarod. Animals were placed on the rotarod, and an accelerating speed was applied from 4-40 rpm over 5 minutes; the time to fall was recorded
- $GABA_A$ receptor positive allosteric modulator (PAM) recordings were conducted by Eurofins Scientific against the human α1β3γ2 receptor. The 10% effect concentration (EC_{10}) of $GABA_A$ (0.85 μM) was added to establish a baseline response, and then 10 μM ezogabine (n = 2) or BHV-7000 (n = 2) was applied in the presence of GABA for 2 seconds
- In a phase 1 SAD/MAD clinical trial of BHV-7000, single doses (up to 100 mg) and multiple doses (up to 40 mg) daily were studied
- Error bars on all graphs represent the standard deviation

IN VITRO RESULTS

Potent Activator of Kv7.2/7.3

- BHV-7000 is a potent activator of Kv7.2/7.3 channels with a half maximal effective concentration (EC_{50}) = 0.6 μM
- BHV-7000 shifts the voltage dependence of activation of Kv7.2/7.3 channels to -21 mV at 3 μM

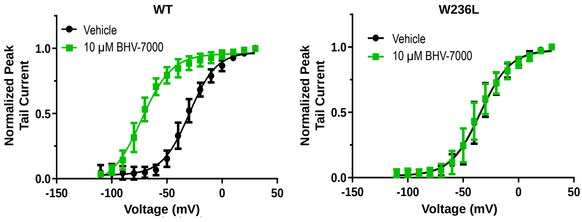




	0.3 μM	1.0 μM	3.0 μM
$V_{1/2}$ shift	-7.6	-15.2	-21.0

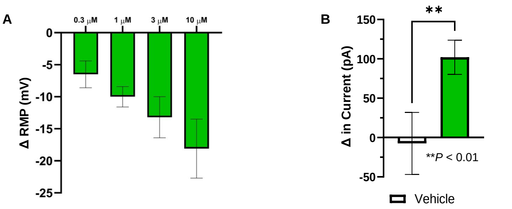
BHV-7000 Requires W236 for Activity

- BHV-7000 shifts the voltage dependence of activation of wild-type (WT) Kv7.2 channels
- All activity is lost in the presence of the W236L mutation. W236 is also required for ezogabine activity



Effects on RMP and AP Threshold

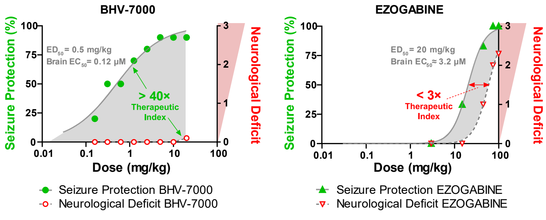
- **(A)** In primary rat cortical neurons, BHV-7000 produced a concentration-dependent hyperpolarization of the RMP
- **(B)** BHV-7000 also significantly increased the AP threshold (P = 0.0058, unpaired t test with Welch's correction)



IN VIVO RESULTS

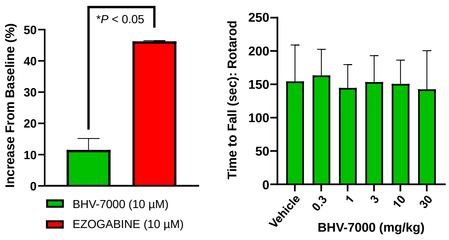
In Vivo Efficacy and No Neurobehavior Effects

- 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, 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

- The $GABA_A$ 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

MedDRA System Organ Class	Placebo (n = 15) n (%)	BHV-7000 (n = 46) n (%)
Nervous system disorders	1 (6.7)	7 (15.2)
Gastrointestinal disorders	1 (6.7)	6 (13.0)
Musculoskeletal disorders	0	5 (10.9)
Infections	0	2 (4.3)
Investigations	1 (6.7)	2 (4.3)
Respiratory disorders	0	2 (4.3)
Skin disorders	0	2 (4.3)
Eye disorders	0	1 (2.2)
General disorders	0	1 (2.2)
Procedural complications	1 (6.7)	1 (2.2)
Psychiatric disorders	0	1 (2.2)
Renal disorders	1 (6.7)	1 (2.2)

MedDRA, Medical Dictionary for Regulatory Activities.

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