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 α13β2γ2δ amiloridic 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 mediate neuronal excitability

Although the Kv7.2/7.3 channel is a validated target for treating seizures, mood disorders 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 electromyography spectral power (see AES 2023 late-breaking poster 2.510)

IN VITRO METHODS / RESULTS

Potent Activator of Kv7.2/3

- 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 (EC50) of 0.6 µM
- (B) BHV-7000 produced a concentration-dependent change in deactivation kinetics (tail tau) and significantly increased deactivation kinetics at 1 µM and above (one-way analysis of variance, Dunnett’s test: p = 0.0115)

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 at 10 µM
- All activity is lost in the presence of the W236L mutation

BHV-7000 is a potent activator of Kv7.2 and Kv7.3 channels

Effects on RMP and AP Threshold

- Protection against seizures was assessed in the MES test using male Wistar rats. Data for BHV-7000 (n = 10/group) and ezogabine (n = 8/group) were collected in independent experiments conducted by Inreko 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 0-5

Potent Activation of Kv7.2/3

- Peak tail currents were measured at 0 mV after activating pulses from -30 mV, followed by a deactivating pulse at -70 mV
- BHV-7000 produced a concentration-dependent change in deactivation kinetics (tail tau) and significantly increased deactivation kinetics at 1 µM and above (one-way analysis of variance, Dunnett’s test: p = 0.0115)

In Vivo Efficacy and No Neurobehavior Effects

- 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 motor performance up to 30 mg/kg

Off-Target and Additional Tolerability Measures

- GABA_A receptor positive allosteric modulator (PAM) recordings were performed against the human α1β2δ receptor expressing cells were treated with 10 µM BHV-7000 (n = 3/group)
- The GABA_A receptor PAM potentiation of BHV-7000 was significantly lower than ezogabine (P = 0.0469, unpaired t-test with Welch’s correction)

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

- GABA_A receptor PAM potentiation of BHV-7000 was significantly lower than ezogabine (P = 0.0469, unpaired t-test with Welch’s correction)

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 = 0.066, unpaired t-test with Welch’s correction)

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 = 8/group) were collected in independent experiments conducted by Inreko 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 0-5
- The concentration of BHV-7000 was significantly lower than ezogabine (P = 0.0469, unpaired t-test with Welch’s correction)

- BHV-7000 protects against MES-induced seizures, with a median effective dose (ED50) of 0.5 mg/kg, while having no impact on neurobehavior and producing a therapeutic index >40
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