INTRODUCTION

The Kv7 (KCNN) 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 epithelium1. Kv7/2.7/3 channels are low-threshold voltage-gated potassium channels expressed in the central nervous system (CNS) that modulate neuronal excitability2. 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. Preclinical 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.

METHODS AND RESULTS

Effects of BHV-7000 on V1/2

- Kv7/2.7/3 channels stably expressed in L2-05 cells were used and examined on the QPatch48 Automated Patch Clamp system1.
- 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 (V1/2) for each cell (I/Imax).
- 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).

Voltage Dependence of Activation

<table>
<thead>
<tr>
<th>Concentration (µM)</th>
<th>Voltage (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 µM</td>
<td>1.9 µM</td>
</tr>
<tr>
<td>3.0 µM</td>
<td>0.3 µM</td>
</tr>
</tbody>
</table>

V1/2 shift

-7.60 -15.21 -20.97

GABAA α1β3γ2 Receptor Activation

- The EC50 concentration of GABA (1.85 mM) was added to establish a baseline response (Table 2).
- Then 10 µM oxagabine (n=2) or BHV-7000 (n=2) was applied in the presence of GABA for 2 seconds. BHV-7000 and oxagabine produced respective potentiation of 12% and 46% (Figure 3).
- The GABAα antagonist BHV-7000 was significantly lower than oxagabine (p=0.0496; unpaired t-test with Welch's correction) (Figure 3).

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.

DISCUSSION

CONCLUSIONS

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

References:

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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 oxagabine (n=10/group) were collected in independent experiments conducted by InterVivo Solutions.
- MES testing was performed at the approximate Cmax for BHV-7000 (1 h after oral dosing) and for oxagabine (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.

BHV-7000 Phase 1 Safety and Tolerability

- In a Phase 1 SAD/MAD clinical trial of BHV-7000, single doses (up to 100 µg) and multiple doses (up to 40 µg) 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 in the MAD Pooled Population

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>MAD pooled (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>18%</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0%</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0%</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>0%</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>0%</td>
</tr>
</tbody>
</table>

BHV-7000 MAD (0-17) (n=17)

Table 1. Voltage Dependence of Activation

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