OBJECTIVE AND METHODS

Objective

Evaluate the safety and tolerability of single- and multiple-ascending doses (SAD and MAD) of oral BHV-7000 in healthy subjects

Methods

A first-in-human, phase 1, single-center, double-blind, placebo-controlled, sequential SAD-MAD study in healthy adults was conducted

SAD subjects were randomized 3:1 to BHV-7000 (10, 25, 50, or 100 mg) or placebo under fasting conditions

- Subjects in the 25-mg SAD cohort received study drug under both fasting and fed conditions

RESULTS

Demographics and baseline characteristics are presented in Table 1

- Mean age in the SAD and MAD cohorts was 40.1 and 40.0 years, respectively
- The majority of subjects were male (87%, MAD, 91%) and white (SAD, 95%; MAD, 91%)

Safety and Tolerability

In the SAD cohort, the most common treatment-emergent AEs (TEAEs) were headache and abdominal discomfort (Table 2)

Across the dosing groups in the SAD and MAD cohorts, there were low rates of nervous system TEAEs

There were no serious TEAEs, severe TEAEs, nor deaths reported in this study

There were no clinically meaningful trends in laboratory values, nor were there clinically meaningful trends or treatment-related findings identified for vital signs, ECGs, or S-STS

DISPOSITION

In the SAD and MAD cohorts, 61 subjects received BHV-7000 (n = 46) or placebo (n = 15)

- The SAD cohort included 39 subjects randomized to BHV-7000 or placebo

- The MAD cohort included 22 subjects randomized to BHV-7000 or placebo

CONCLUSIONS

BHV-7000 was safe and well tolerated at single doses up to 100 mg and multiple doses up to 120 mg daily for 15 days

Adverse events (AEs) typically associated with other anti-seizure medications (ASMs), such as somnolence and cognitive/mood disturbances, were not reported, which represents a potential paradigm shift in epilepsy treatment

These findings support the continued clinical development of BHV-7000 in epilepsy

INTRODUCTION

Approximate one-third of people with epilepsy are refractory to treatment, despite the availability of ASMs, surgery, and dietary therapies

AEs associated with ASMs, such as somnolence and cognitive/mood disturbances, can impact quality of life and treatment adherence

BHV-7000 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels, a clinically validated target in epilepsy

In preclinical studies, BHV-7000 showed minimal gamma-aminobutyric acid type A (GABA\(_A\)) receptor activation and inhibited potential anti-epileptic efficacy in the chronic electroshock-seizure model without negatively impacting neurobehavior or motor function (see AES 2023 poster 2.242)\(^a\)

The pharmacodynamic activity of BHV-7000 in the brain of healthy adults was demonstrated in a phase 1 study by dose-dependent increases in electroencephalograph spectral power (see AES 2023 poster 2.510)

A first-in-human, phase 1, single-center, double-blind, placebo-controlled, sequential SAD-MAD study in healthy adults was conducted

SAD subjects were randomized 3:1 to BHV-7000 (10, 25, 50, or 100 mg) or placebo and dosed for 15 days

Across the dosing groups in the SAD and MAD cohorts, there were low rates of nervous system TEAEs

There were no serious TEAEs, severe TEAEs, nor deaths reported in this study

The majority of TEAEs were mild in severity and resolved by the conclusion of the study

There were no clinically meaningful trends in laboratory values, nor were there clinically meaningful trends or treatment-related findings identified for vital signs, ECGs, or S-STS

All TEAEs reported in the MAD cohorts were mild in severity, except 1 case of back pain in 40 mg, 1 case of dizziness, moderate severity, 10 mg (Fasted), and 1 case of headache, mild severity, 10 mg (Fed)

*Data are included from a separate study evaluating higher MAD doses.

AEs associated with ASMs, such as somnolence and cognitive/mood disturbances, were not reported, which represents a potential paradigm shift in epilepsy treatment

These findings support the continued clinical development of BHV-7000 in epilepsy

Table 1. Subject Demographics and Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single-Ascending Dose</th>
<th>Multiple-Ascending Dose</th>
</tr>
</thead>
</table>
| Mean (SD) BMI, kg/m\(^2\) | 25 mg (Fed) | 7000 (10, 25, or 40 mg daily) or placebo and dosed for 15 days

Key inclusion criteria

- Healthy male or nonchildbearing female subjects ≥18 and ≤55 years of age
- Body mass index (BMI) ≥18.0 and ≤30.0 kg/m\(^2\)
- Body weight ≥55.0 kg

Safety evaluations included AE monitoring, clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, and Sheehan Suicidality Tracking Scale (S-STS) score

A safety review committee assessed the safety and tolerability after completion of each dose level prior to dose escalation

Table 2. TEAEs Occurring in 22 Subjects Receiving BHV-7000 in the SAD Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0(\times 0)</td>
</tr>
<tr>
<td>Nervous System AEs</td>
<td>BHV-7000</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System AEs</td>
<td>BHV-7000</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal AEs</td>
<td>BHV-7000</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System AEs</td>
<td>BHV-7000</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are included from a separate study evaluating higher MAD doses.

All TEAEs reported in the SAD cohorts were mild in severity and resolved.