INTRODUCTION

Neuroactive steroids (NASs) can function as positive allosteric modulators (PAM) of synaptic and extrasynaptic GABA\(_A\) receptors intended for once daily, oral dosing. A prior, multiple ascending dose study in healthy volunteers showed linear, dose-dependent changes in the power of EEG beta band, a hallmark of GABA modulation, indicating target engagement at doses as low as 15 mg. Pharmacokinetic data from separate single ascending dose and multiple ascending dose studies demonstrate that SAGE-217 is compatible with once daily, oral dosing. This was the first clinical trial with SAGE-217 in subjects with MDD. The study’s modest number of subjects and open-label design prevent strong conclusions; however, the encouraging results warrant further investigation of SAGE-217 in subjects with MDD.

METHODS

Part A of this study included male and female subjects aged 18–65 years with MDD present for at least 4 weeks; moderate- to-severe MDD, as determined by a Hamilton Rating Scale for Depression (HAM-D) score of ≥22; subjects with a history of treatment-resistant depression were excluded. Safety and tolerability were assessed via standard safety parameters, including adverse events (AEs). Doses provided as a 40 mL aqueous solution; stock SAGE-217 solution was 6 mg/mL, with hydroxypropyl-β-cyclodextrin and sucrose. Subjects received open-label, single, nightly (8PM) doses of 30 mg SAGE-217 oral solution on Days 1–14. Depressive symptoms were assessed by the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS), and anxiety symptoms via the Hamilton Anxiety Rating Scale (HAM-A) at 8AM (+/- 30 minutes). LS Means, SEs, and p-values were based on a mixed effects model for repeat measurements with visit as a fixed effect, adjusting for baseline total MADRS score, with AR(1) covariance structure.

This trial is registered at ClinicalTrials.gov under NCT03000530 (https://clinicaltrials.gov/ct2/show/NCT03000530).

OBJECTIVES

• To evaluate the safety and tolerability of SAGE-217 in subjects with MDD.
• To determine if treatment with SAGE-217 for 14 days reduced depressive symptoms in subjects with MDD.

RESULTS

SAGE-217 in Subjects with Major Depressive Disorder: Efficacy and Safety Results from Open-label Part A of a Phase 2a Study

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INTRODUCTION

GABA, benzodiazepines, and barbiturates. NASs can bind to both synaptic and extrasynaptic GABA\(_A\) receptors (Figure 1), and altered levels of NASs have been implicated in depressive disorders.6

SAGE-217 is a novel positive allosteric modulator (PAM) of synaptic and extrasynaptic GABA\(_A\) receptors for once daily, oral dosing. A prior, multiple ascending dose study in healthy volunteers showed linear, dose-dependent changes in the power of EEG beta band, a hallmark of GABA modulation, indicating target engagement at doses as low as 15 mg. Pharmacokinetic data from separate single ascending dose and multiple ascending dose studies demonstrate that SAGE-217 is compatible with once daily, oral dosing.7,8

Figure 1. Positive allosteric regulation of GABA\(_A\) receptors. GABA\(_A\)Rs are located in synaptic and extrasynaptic regions. Binding sites for NASs are distinct from the recognition sites for GABA, benzodiazepines, and barbiturates. NASs can bind to both synaptic and extrasynaptic GABA\(_A\) receptors.

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This trial is registered at ClinicalTrials.gov under NCT03000530 (https://clinicaltrials.gov/ct2/show/NCT03000530).

RESULTS

SAGE-217 Part A Design. This study was an open-label, 13 subject, Part A of a Phase 2 study.

13 subjects moderate to severe MDD

SAGE-217 30mg QD PO

Day 2

Primary Endpoint

Day 15

Follow-up

Day 28

Inpatient

Outpatient

Days 1-7

Days 8-14

Open-label

Figure 2. SAGE-217 Part A Design. This study was an open-label, 13 subject, Part A of a Phase 2 study.

Table 1. Demographics. A total of 13 subjects were enrolled. The mean age was 48 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Race</th>
<th>Baseline Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Female</td>
<td>Hispanic/Latino</td>
<td>Not Hispanic/Latino</td>
<td>HAM-D</td>
</tr>
<tr>
<td>48 (12.83)</td>
<td>9 (69.2%)</td>
<td>1 (7.7%)</td>
<td>12 (92.3%)</td>
<td>27.2 (3.06)</td>
</tr>
</tbody>
</table>

Table 2. Treatment-Emergent Adverse Events (TEAEs). There were no deaths, serious TEAEs, severe TEAEs, or TEAEs leading to study withdrawal.

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Days 1-7</th>
<th>Days 8-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>6 (46.2%)</td>
<td>6 (46.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (30.8%)</td>
<td>4 (30.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (23.1%)</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (23.1%)</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (23.1%)</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>2 (15.4%)</td>
<td>2 (15.4%)</td>
</tr>
</tbody>
</table>

Figure 3. HAM-D Total Scores. N=13 per time point.

Figure 4. MADRS Scores. N=13 per time point.

Figure 5. HAM-A Total Scores. N=13 per time point.

Figure 6. HAM-D Response and HAM-D Remission Rates. Response was defined as a 50% or greater reduction from baseline in HAM-D score. Remission was defined as a reduction in HAM-D total score to ≤7. N=13 per time point.

Conclusions and Implications

• This was the first clinical trial with SAGE-217 in subjects with MDD. There were no serious or severe AEs or AEs leading to study withdrawal. Subjects demonstrated mean improvement in depressive symptoms 1 day following initiation of dosing, throughout the dosing period, and for 2 weeks after cessation of dosing.
• This study’s modest number of subjects and open-label design prevent strong conclusions; however, the encouraging results warrant further investigation of SAGE-217 in subjects with MDD. Part B of this trial – a randomized, double-blind, placebo-controlled study with a solid oral dose – is ongoing (ClinicalTrials.gov Identifier: NCT03000530).

REFERENCES


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DISCLOSURES

Handan Gunduz-Bruce, George Nomikos, Abdul 1. Sankoh, Hailong Li, James Doherty, and Stephen Kanes are employees of Sage Therapeutics, Inc.