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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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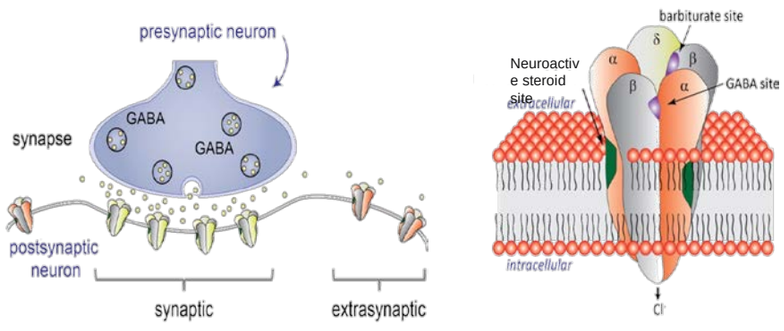
Introduction and Objectives

INTRODUCTION

- The prevalence of major depressive disorder (MDD) is estimated to be 16.2%; national population projections reveal approximately 33 million adults in the US living with MDD.[1]
- Antidepressants are associated with side-effects[2] and variable efficacy,[3] with remission in fewer than half of MDD patients.[4,5]
- Studies have suggested a role for GABA signaling in a variety of disease states, including mood disorders such as MDD.
- Neuroactive steroids (NASs) can function as positive allosteric modulators (PAM) of 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 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.[7]
- 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



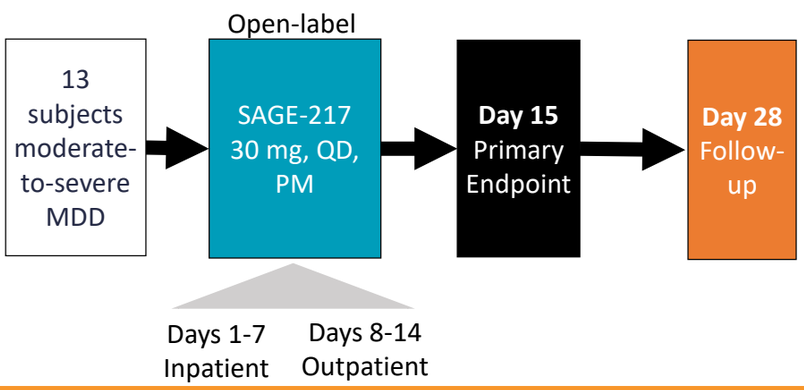
OBJECTIVES

- 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.

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 sucralose.
- 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).

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



Results

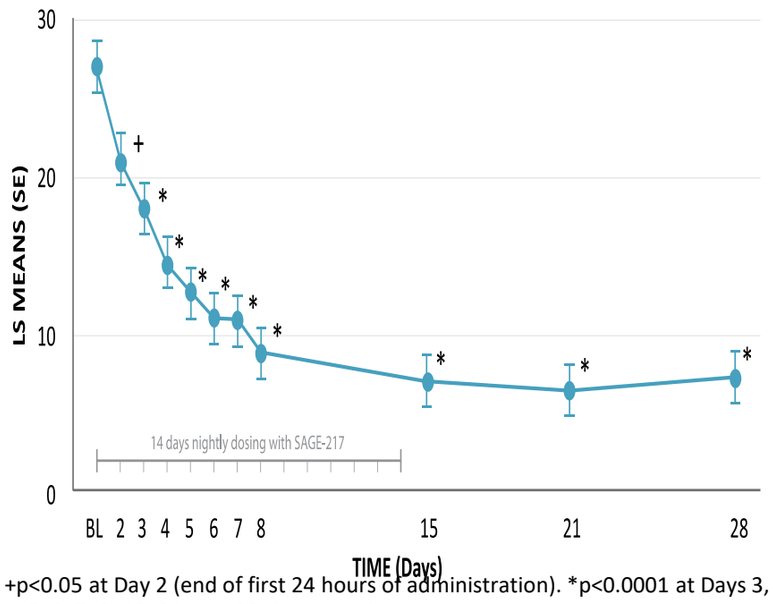
Table 1. Demographics. A total of 13 subjects were enrolled. The mean age was 48 years.

	Statistic	Total (N=13)
Age	Mean (SD)	48 (12.83)
Sex	Female	9 (69.2%)
	Male	4 (30.8%)
Ethnicity	Hispanic/Latino	1 (7.7%)
	Not Hispanic/Latino	12 (92.3%)
Race	Black or African American	9 (62.9%)
	White	4 (30.8%)
Baseline Scores [Mean (SD)]	HAM-D	27.2 (3.06)
	MADRS	36.9 (5.22)
	HAM-A	23.2 (5.65)

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

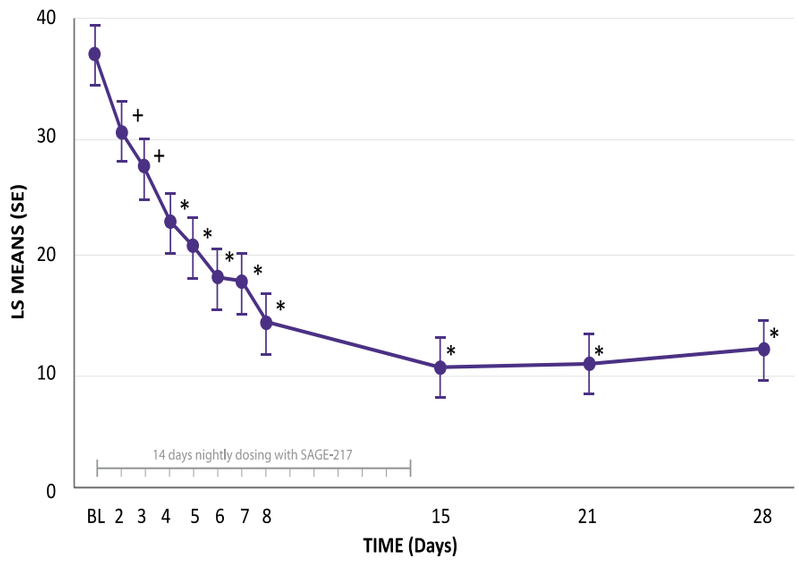
	SAGE-217 (N=13)
Overall Summary	
At least one AE	12 (92.3%)
Drug-related AE	11 (84.6%)
Severe AE	0
Serious AE	0
AE leading to drug discontinuation	0
AE leading to death	0
AEs in at Least Two Subjects	
Sedation	6 (46.2%)
Headache	4 (30.8%)
Dizziness	3 (23.1%)
Somnolence	3 (23.1%)
Myalgia	3 (23.1%)
Nasal Congestion	2 (15.4%)

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



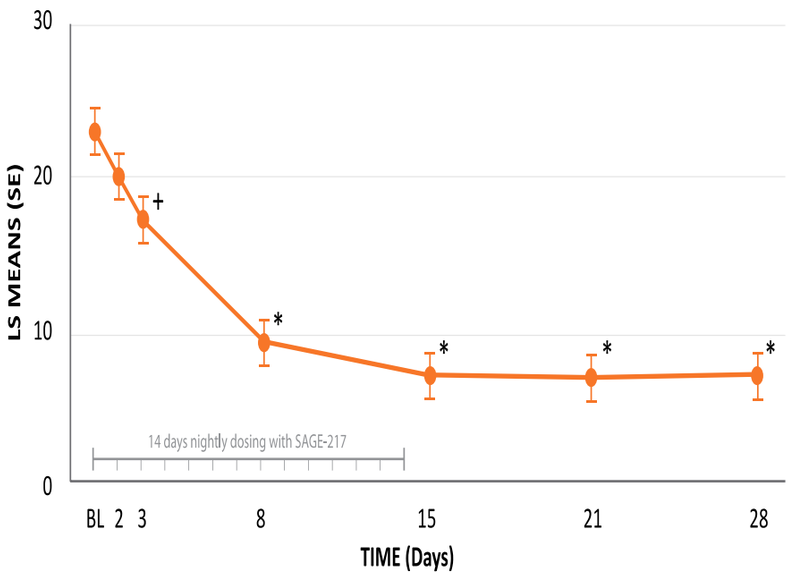
+p<0.05 at Day 2 (end of first 24 hours of administration). *p<0.0001 at Days 3, 4, 5, 6, 7, 8, 15, 21, and 28. BL = baseline

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



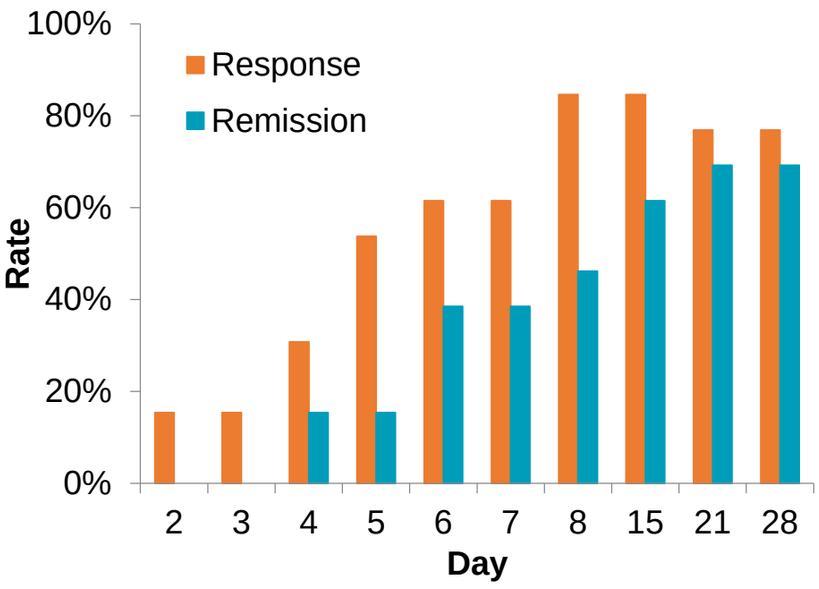
+p<0.05 for Days 2 (end of first 24 hours of administration) and 3. *p<0.0001 for Days 4, 5, 6, 7, 8, 15, 21, and 28. BL = baseline

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



+p<0.05 at Day 3. *p<0.0001 at Days 8, 15, 21, and 28. BL = baseline

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).

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