

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. *N Engl J Med* 2019;381:903-11. DOI: 10.1056/NEJMoa1815981

SUPPLEMENTARY FILES FOR: TRIAL OF SAGE-217 IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Randomized, double-blind, placebo-controlled methods:

Inclusion criteria:

The following inclusion criteria must be met for individuals to be eligible for the study.

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.
5. Subject has a diagnosis of MDD that has been present for at least a 4-week period as diagnosed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I).
6. Subject has a HAM-D total score of ≥ 22 at screening and Day 1 (prior to dosing).
7. Removed per Amendment #2.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, during the screening and treatment periods.
9. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study

drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence (no sexual intercourse).

Exclusion criteria:

Subjects will be excluded if they meet any of the following exclusion criteria:

1. Subject has a history of suicide attempt.
2. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
3. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants

from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).

4. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.

5. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.

6. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening (except if the subject has a documented Hepatitis C antigen test (HCV RNA) with a negative result in their recent medical history).

7. Subject has active psychosis per Investigator assessment.

8. Subject has a medical history of seizures.

9. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

10. Subject has a history of alcohol or drug dependence (including benzodiazepines) in the 12 months prior to screening.

11. Subject has had exposure to another investigational medication or device within 30 days prior to screening.

12. Subject has been treated or randomized in this study (eg, Part A) or any other study employing SAGE-217 previously (ie, subject may not have received study drug and then re-enroll).

13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose in

Part A. Subject has had administration of psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have been initiated within 30 days prior to screening and/or are not being taken at a stable dose in Part B.

14. Use of any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

15. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.

Open-label study methods:

Study design and participants:

The open-label study of SAGE-217 in MDD was conducted at two sites in the United States. IRB approval was obtained at each study site. Sage Therapeutics, Inc. designed the trial and collaborated with all investigators in the execution of the trial and collection of data. All authors vouch for the accuracy and completeness of the data, data analyses, reporting of adverse events, and the fidelity of this publication to the study protocol.

Study population:

The study population included subjects of both sexes, ages 18-65 years, with a diagnosis of MDD, and a Hamilton Rating Scale for Depression (HAM-D) total score of ≥ 22 . Written informed consent was provided at screening and was required for

enrollment. MDD diagnoses were made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I), as performed by a qualified healthcare professional. Key exclusion criteria included a history of suicide attempt, history of treatment-resistant depression (defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time [i.e. at least 4 weeks of treatment]), recent history or active clinically significant manifestations of other acute or chronic conditions, positive pregnancy test, history of seizures, medical history of bipolar disorder, schizophrenia, and (or) schizoaffective disorder. Subjects were allowed to remain on a stable dose of psychotropic medications that were initiated at least 14 days prior to screening. Following completion of the treatment period, subjects were allowed to begin or alter antidepressant regimens.

Inclusion and exclusion criteria:

The following inclusion criteria must be met for individuals to be eligible for the study.

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory male or female between 18 and 65 years of age, inclusive.
3. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Subject agrees to adhere to the study requirements.

5. Subject has a diagnosis of MDD that has been present for at least a 4-week period as diagnosed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Axis I Disorders (SCID-I).
6. Subject has a HAM-D total score of ≥ 22 at screening and Day 1 (prior to dosing).
7. Removed per Amendment #2.
8. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, during the screening and treatment periods.
9. Subject agrees to practice an acceptable method of highly effective birth control at screening and throughout study participation. Highly effective methods of birth control include sexual abstinence (for males and females); vasectomy; or a condom with spermicide in combination with a highly effective female partner's method (for males); and hormonal methods of contraception (ie, established use of oral, implantable, injectable, or transdermal hormones); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream, or suppository]) (for females).

Exclusion criteria included:

Subjects will be excluded if they meet any of the following exclusion criteria.

1. Subject has a history of suicide attempt.

2. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
3. Subject has a history of treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment).
4. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
5. Subject has a positive pregnancy test at screening or on Day 1 prior to the start of study drug administration.
6. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) antibody at screening (except if the subject has a documented Hepatitis C antigen test (HCV RNA) with a negative result in their recent medical history).
7. Subject has active psychosis per Investigator assessment.
8. Subject has a medical history of seizures.
9. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.

10. Subject has a history of alcohol or drug dependence (including benzodiazepines) in the 12 months prior to screening.
11. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
12. Subject has been treated or randomized in this study (eg, Part A) or any other study employing SAGE-217 previously (ie, subject may not have received study drug and then re-enroll).
13. Subject has had administration of psychotropics that have been initiated within 14 days prior to screening and/or are not being taken at a stable dose in Part A.
14. Use of any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
15. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing

Procedures:

Open-label study subjects received an open-label 30 mg dose of SAGE-217 oral solution at 8:00PM (\pm 15 minutes) with food on Days 1 through 14. Subjects remained as inpatients during the first 7 days of each study period and per the Investigator's judgment thereafter through Day 15. Treatment follow-up was conducted on an outpatient basis and included a follow-up visit at 1 week (21 ± 1 day) and at 2 weeks (28 ± 1 day) after the last dose of the study drug.

Outcomes:

The primary endpoint of the open-label study was safety and tolerability. Safety and tolerability were assessed by the frequency and severity of adverse events, vital signs, changes in clinical laboratory measures, physical exams, electrocardiograms (ECGs), the Stanford Sleepiness Scale (SSS) score, and assessment of suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS). Treatment emergent adverse events (TEAEs) were defined as AEs or any worsening of a pre-existing medical condition with onset after the start of study drug until 7 days after the last dose. Efficacy was assessed by the HAM-D, Montgomery-Åsberg Depression Rating Scale (MADRS), and Hamilton Anxiety Rating Scale (HAM-A), including categorical responses, such as HAM-D response ($\geq 50\%$ reduction) and HAM-D remission (total score ≤ 7).

Statistical Analysis:

Continuous parameters were summarized as n, mean, and standard deviation, with categorical variables summarized as frequency counts and percentages.

Open-label study results:

The demographic characteristics are provided in Supplemental Table 1 (Table S1). The mean age was 48 (12.8) and majority of the patients were female and African American. SAGE-217 treatment was generally well tolerated, and there were no serious adverse events (SAEs) or discontinuations due to AEs (Table S2). The most common AEs (≥ 4

subjects) were sedation and headache (Table S2). One more AE (tooth abscess) was reported in the rest of the follow-up period.

Following treatment with SAGE-217, reduced depressive symptoms were observed at Day 15 by the HAM-D total score (the primary efficacy endpoint), with a mean decrease from baseline of -19.9 (Supplemental Figure S1). HAM-D total score reductions were present as early as Day 2 and were maintained through the conclusion of the study, two weeks after study drug discontinuation (Day 28; Supplemental Figure S1). In 11 of 13 subjects (85%), the HAM-D total score was reduced by least 50% (HAM-D response) at Day 15 compared to baseline, and this HAM-D response was sustained through Day 28 (Supplemental Figure S2). In 8 of 13 subjects (62%), the HAM-D total score was ≤ 7 at the end of the treatment period (HAM-D remission), and remission was sustained through Day 28 (Supplemental Figure S2). MADRS scores were consistent with HAM-D results, with a mean total decrease from baseline of -26.4 at Day 15 (Supplemental Figure S1). Reduced anxiety symptoms were also observed by the HAM-A, with a mean decrease from baseline of -15.5 (Supplemental Figure S1) at Day 15 that was sustained to Day 28 (Supplemental Figure S1).

Additional double-blind, randomized, placebo-controlled trial details:**Bracket Qualification Methodology in the double-blind, randomized, placebo-controlled trial:**

Three categories of services including experience, performance, and analysis/remediation were delivered to provide quality rater training and ensure consistent ratings throughout the trial. To qualify as a rater for the administration of the SCID, HAM-D, HAM-A, MADRS, and CGI, raters had to have advanced degrees (MD, DO, or masters level or equivalent in a medical or psychology related field), at least 2 years of clinical and scale administration experience in major depressive disorder, and experience with greater than 5 administrations of SCID, 10 administrations of HAM-D, HAM-A, and MADRS, and 20 administrations of CGI in the last 12 months.

CGI-I Response Results in the double-blind, randomized, placebo-controlled trial:

At Day 15, the percentage of patients who met CGI-I response criteria was greater in the SAGE-217 group than in the placebo group (78.6% vs. 45.2%; odds ratio 8.6, unadjusted 95% CI, 2.5 to 29.5) (Figure S7; Table S8).

HAM-A Results in the double-blind, randomized, placebo-controlled trial:

Reductions in anxiety symptoms were also observed favoring SAGE-217 treatment, as assessed by the HAM-A. At Day 15, the least squares mean (SE) change from baseline in HAM-A total score was -13.2 (1.1) for the SAGE-217 group and -8.6 (1.1) for the placebo group, with an LS mean difference of -4.6 (unadjusted 95% CI, -7.3 to -2.0) (Figure S8; Table S9).

Supplemental Tables and Figures:

Supplemental Table 1. Demographics in the open-label study of SAGE-217 in MDD.

Characteristics	SAGE-217 (n=13)
Age (years), mean (SD)	48.0 (12.8)
Gender	
Female, n (%)	9 (69.2%)
Race	
American Indian or Alaska Native, n (%)	0
Asian, n (%)	0
Black or African American, n (%)	9 (69.2%)
Native Hawaiian/Pacific Islander, n (%)	0
White, n (%)	4 (30.8%)
Other, n (%)	0
Body Mass Index (kg/m ²), mean (SD)	32.2(6.0)
Baseline HAM-D Score, mean (SD)	27.2 (3.1)
Baseline Antidepressant use	5 (38.5)

Supplemental Table 2. Treatment emergent adverse events (TEAEs) reported by 3 or more patients in the open-label study of SAGE-217 in MDD, reported as n (%).

	TEAEs SAGE-217 (n=13)
Patients with at least one TEAE	12 (92.3%)
Patients with serious AEs	0
Patients with severe AEs	0
TEAEs reported by 3 or more patients	
Sedation	6 (46.2%)
Headache	4 (30.8%)
Dizziness	3 (23.1%)
Somnolence	3 (23.1%)

Supplemental Table 3: Duration of prior antidepressant therapy in patients receiving antidepressant therapy in the double-blind randomized, placebo-controlled trial.

Duration of Antidepressant Treatment	Placebo (n=10) n (%)	SAGE-217 (n=12) n (%)
<8 weeks	0	0
2-6 months	5 (50)	3 (25)
6-12 months	0	2 (17)
12-24 months	1 (10)	4 (24)
24-48 months	1 (10)	2 (17)
>48 months	3 (30)	1 (8)

Supplemental Table 4. Results from the sensitivity analyses on the primary endpoint at Day 15, based on two different imputation methods: multiple imputation (using a fully conditional specification regression method) and last observation carried forward (using the last observed non-missing value).

	LS Mean for SAGE-217 (N=45)	LS Mean for Placebo (N=44)	LS Mean Difference (SE)	95% CI	p- value
Primary model	-17.4 (1.3)	-10.3 (1.3)	-7.0 (1.6)	-10.2 to - 3.9	<0.001
Multiple imputation	-17.3 (1.3)	-10.3 (1.3)	-7.0 (1.6)	-10.1 to - 3.9	<0.001
Last observation carried forward	-17.2 (1.3)	-10.3 (1.3)	-6.9 (1.6)	-10.1 to - 3.7	<0.001

Supplemental Table 5: HAM-D total score, response, and remission statistics in the double-blind, randomized trial of SAGE-217. HAM-D total score least-squares (LS) means were calculated using a mixed effects model for repeated measures (MMRM). HAM-D response and remission were analyzed using generalized estimating equation (GEE) models. LS means are presented with standard errors (SE). The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes (i.e. HAM-D Total Score changes on Days 2-8, 21, 28, 35, 42; HAM-D Response and Remission).

	HAM-D Total Score				HAM-D Response				HAM-D Remission			
	SAGE-217 (N=45)	Placebo (N=44)	LS means difference	95% CI	SAGE-217 (N=45)	Placebo (N=44)	Odds Ratio	95% CI	SAGE-217 (N=45)	Placebo (N=44)	Odds Ratio	95% CI
Day 2	-5.8 (0.97)	-3.5 (0.98)	-2.3 (0.99)	-4.3 to -0.3	16%	5%	4.4	0.8 to 24.1	2%	0%	N/A	N/A
Day 3	-9.3 (1.07)	-5.2 (1.09)	-4.1 (1.18)	-6.4 to -1.7	33%	9%	6.8	1.9 to 23.8	13%	2%	6.8	0.8 to 61.8
Day 4	-10.6 (1.11)	-7.7 (1.13)	-2.9 (1.27)	-5.5 to -0.4	40%	26%	2.5	0.9 to 6.8	16%	7%	2.6	0.6 to 11.3
Day 5	-12.3 (1.17)	-8.5 (1.19)	-3.8 (1.37)	-6.6 to -1.1	58%	32%	4.5	1.7 to 11.9	16%	14%	1.2	0.4 to 3.9
Day 6	-13.6 (1.19)	-9.1 (1.21)	-4.5 (1.40)	-7.3 to -1.7	64%	39%	4.6	1.7 to 12.0	38%	14%	3.9	1.3 to 11.4
Day 7	-13.7 (1.27)	-9.2 (1.29)	-4.5 (1.53)	-7.6 to -1.5	60%	42%	3.3	1.2 to 8.9	33%	14%	3.2	1.1 to 9.4
Day 8	-14.4 (1.27)	-11.0 (1.29)	-3.4 (1.54)	-6.4 to -0.3	59%	48%	2.4	0.9 to 6.4	36%	29%	1.5	0.6 to 3.7
Day 15	-17.4 (1.31)	-10.3 (1.33)	-7.0 (1.60)	-10.2 to -3.9	79%	41%	9.6	2.9 to 31.6	64%	26%	5.3	2.1 to 13.3
Day 21	-16.3 (1.40)	-11.3 (1.43)	-4.9 (1.76)	-8.4 to -1.4	74%	42%	6.7	2.3 to 19.7	52%	26%	3.1	1.2 to 8.0
Day 28	-15.4 (1.41)	-11.3 (1.44)	-4.1 (1.77)	-7.6 to -0.5	62%	46%	3.1	1.1 to 8.9	52%	28%	2.9	1.2 to 7.3
Day 35	-14.9 (1.47)	-12.6 (1.49)	-2.3 (1.86)	-6.0 to 1.4	66%	50%	3	1.0 to 9.0	44%	35%	1.4	0.6 to 3.5
Day 42	-14.6 (1.46)	-12.3 (1.49)	-2.3 (1.86)	-6.0 to 1.4	62%	56%	1.9	0.7 to 5.6	45%	33%	1.7	0.7 to 4.3

Supplemental Table 6. Day 15 HAM-D total score mean change from baseline, HAM-D response ($\geq 50\%$ reduction in total score), and HAM-D remission (total score ≤ 7) stratified by concomitant antidepressant use during the treatment period in the double-blind, randomized, placebo-controlled study. This is a post-hoc descriptive analysis, and no statistical inferences can be made from the data.

	Antidepressant		No antidepressant	
	Placebo (N=10)	SAGE-217 (N=12)	Placebo (N=34)	SAGE-217 (N=33)
Number of patients with available HAM-D total score at Day 15	9	12	33	30
HAM-D Change from Baseline, mean (SD)	-7.7 (7.0)	-17.9 (8.1)	-11.6 (7.9)	-17.5 (7.2)
HAM-D Response, n (%)	2 (22.2%)	10 (83.3%)	15 (45.5%)	23 (76.7%)
HAM-D Remission, n (%)	1 (11.1%)	8 (66.7%)	10 (30.3%)	19 (63.3%)

Supplemental Table 7. Number of patients who received additional antidepressants in the naturalistic follow-up period in the double-blind, randomized, placebo-controlled study (Days 15-42).

	No new antidepressants	New Antidepressants
Placebo	33	11
SAGE-217	42	3

Supplemental Table 8. Montgomery-Åsberg Depression Rating Scale

(MADRS) change over time in the double-blind, randomized, placebo-controlled study. MADRS total scores were recorded as indicated across 42 days. The change from baseline in MADRS total score least squares (LS) means was determined by a mixed model for repeated measures. LS means are presented with standard errors (SE). SAGE-217, n=45; Placebo, n=44. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Day	Placebo (n=44)	SAGE-217 (n=45)	LS Mean Difference	95% CI
2	-4.5 (1.4)	-6.9 (1.4)	-2.4 (1.4)	-5.1 to 0.3
3	-7 (1.5)	-11.8 (1.5)	-4.8 (1.6)	-8.0 to -1.5
4	-9.8 (1.6)	-14 (1.6)	-4.2 (1.8)	-7.8 to -0.6
5	-11.6 (1.7)	-15.6 (1.7)	-4.0 (2.0)	-7.9 to 0.0
6	-12.9 (1.7)	-17.8 (1.6)	-4.9 (1.9)	-8.7 to -1.1
7	-13.3 (1.9)	-18.0 (1.9)	-4.7 (2.3)	-9.2 to -0.2
8	-15.4 (1.9)	-19.4 (1.9)	-4.0 (2.3)	-8.6 to 0.6
15	-15 (1.9)	-22.5 (1.9)	-7.6 (2.4)	-12.3 to -2.8
21	-15.2 (2.1)	-21.9 (2.1)	-6.6 (2.7)	-12.0 to -1.3
28	-14.8 (2.1)	-20.1 (2.1)	-5.3 (2.7)	-10.6 to 0.1
35	-16.4 (2.3)	-19.4 (2.2)	-3.1 (2.9)	-8.8 to 2.6
42	-17.2 (2.1)	-19.1 (2.1)	-2.0 (2.7)	-7.4 to 3.4

Supplemental Table 9: CGI-I Response in the double-blind, randomized, placebo-controlled study. CGI-I response was considered a score of 1 (very much improved) or 2 (much improved) and was analyzed using a generalized estimating equation model. SAGE-217, n=45; Placebo, n=44. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Day	Placebo (n=44)	SAGE-217 (n=45)	Odds Ratio	95% CI
3	7%	40%	16.9	3.5 to 81.5
8	45%	70%	5.5	1.7 to 17.9
15	45%	79%	8.6	2.5 to 29.5
21	50%	71%	4.4	1.4 to 13.6
28	46%	67%	3.9	1.2 to 12.8
35	55%	63%	2.3	0.7 to 7.2
42	59%	69%	2.7	0.9 to 8.3

Supplemental Table 10. HAM-A in the double-blind, randomized, placebo-controlled study. HAM-A total scores were recorded as indicated across 42 days. The change from baseline in HAM-A total score least squares (LS) means was determined by a mixed model for repeated measures. LS means are presented with standard errors (SE). SAGE-217, n=45, Placebo, n=44. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Day	Placebo (n=44)	SAGE-217 (n=45)	LS Means Difference	95% CI
2	-3.7 (0.9)	-5.5 (0.8)	-1.8 (0.9)	-3.6 to -0.1
3	-5.7 (0.9)	-8.3 (0.9)	-2.6 (1.0)	-4.6 to -0.6
8	-8.9 (1.1)	-11.4 (1.1)	-2.5 (1.3)	-5.1 to 0.0
15	-8.6 (1.1)	-13.2 (1.1)	-4.6 (1.3)	-7.3 to -2.0
21	-9.5 (1.3)	-12.9 (1.21)	-3.4 (1.5)	-6.5 to -0.4
28	-10.0 (1.3)	-12.2 (1.2)	-2.2 (1.6)	-5.3 to 0.9
35	-9.9 (1.4)	-12.0 (1.4)	-2.0 (1.8)	-5.5 to 1.5
42	-9.6 (1.4)	-11.8 (1.4)	-2.3 (1.8)	-5.7 to 1.2

Supplemental Table 11. Adverse events (AEs) reported after the treatment-emergent period (Days 21-42). Data are presented as n (%), as indicated.

	SAGE-217	Placebo	Total
	n=45	n=44	n=89
	n (%)	n (%)	n (%)
Patients with at least one AE	4 (8.9)	10 (22.7)	14 (15.7)
Patients with serious AEs	0	0	0
Patients with severe AEs	0	0	0
AEs after the treatment emergent period			
Headache	1 (2.2)	1 (2.3)	2 (2.2)
Nausea	0	2 (4.5)	2 (2.2)
Upper respiratory tract infection	0	2 (4.5)	2 (2.2)
Blood pressure increased	1 (2.2)	0	1 (1.1)
Diarrhea	0	1 (2.3)	1 (1.1)
Flank Pain	0	1 (2.3)	1 (1.1)
Hypothyroidism	1 (2.2)	0	1 (1.1)
Laceration	1 (2.2)	0	1 (1.1)
Myalgia	0	1 (2.3)	1 (1.1)
Oropharyngeal pain	0	1 (2.3)	1 (1.1)
Rhinitis	0	1 (2.3)	1 (1.1)
Sexual dysfunction	0	1 (2.3)	1 (1.1)
Viral infection	0	1 (2.3)	1 (1.1)
Vomiting	0	1 (2.3)	1 (1.1)

Supplemental Table 12. Stanford sleepiness scale (SSS)

The SSS is subject-rated scale designed to quickly assess how alert a subject is feeling. Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of '1' indicates the subject is 'feeling active, vital, alert, or wide awake', the highest score of '7' indicates the subject is 'no longer fighting sleep, sleep onset soon; having dream-like thoughts' and X indicates "Asleep". No scores of "X" were recorded. SAGE-217, n=45; Placebo, n=44. The mean (SD) values are presented.

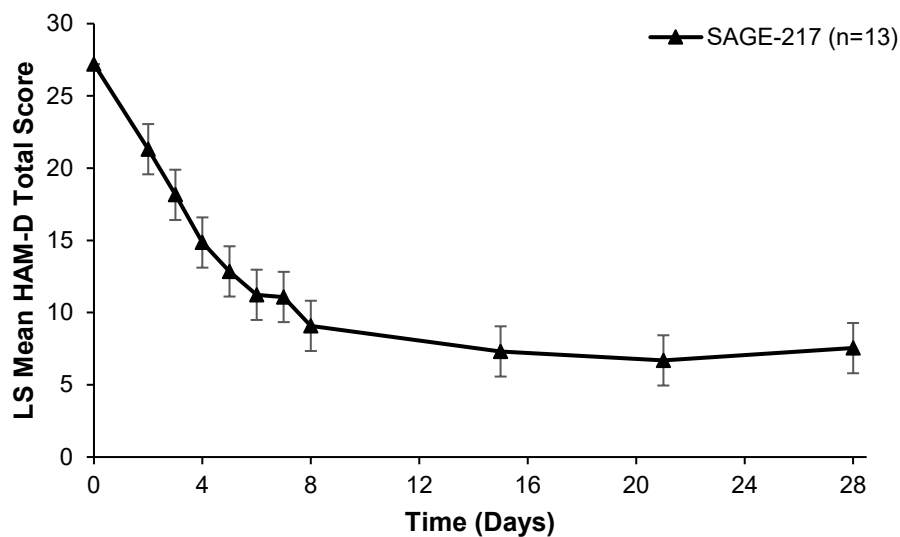
	Time Point	Placebo (n=44)	SAGE-217 (n=45)
Baseline		2.7 (1.5)	2.6 (1.3)
Day 1	1 hour postdose	2.6 (1.4)	2.7 (1.3)
	2 hours postdose	2.6 (1.4)	3.1 (1.5)
Day 7	Predose	1.9 (0.8)	2.0 (1.0)
	1 hour postdose	2.2 (1.1)	2.4 (1.2)
	2 hours postdose	2.4 (1.3)	2.7 (1.2)
Day 14	Predose	2.0 (0.8)	2.0 (1.2)
	1 hour postdose	2.1 (1.0)	2.3 (1.3)
Day 15		2.2 (1.1)	1.8 (1.2)

Supplemental Table 13. Treatment emergent adverse events (TEAEs) reported by 3 or more patients in the double-blind, randomized, placebo-controlled study of SAGE-217 in MDD, reported as n (%).

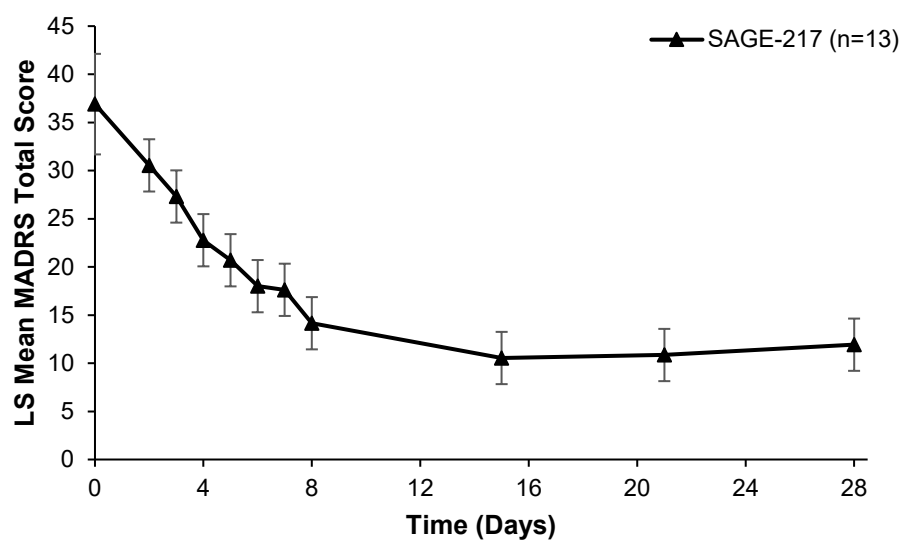
	SAGE-217 - antidepressant (n=12)	SAGE-217 - no antidepressant (n=33)
Any TEAE	8 (66.7%)	16 (48.5%)
Headache	3 (25.0%)	5 (15.2%)
Dizziness	1 (8.3%)	4 (12.1%)
Nausea	2 (16.7%)	3 (9.1%)
Somnolence	2 (16.7%)	1 (3.0%)

Supplemental Figure 1. HAM-D, MADRS, and HAM-A total scores in an open-label study of SAGE-217 in MDD. A. HAM-D total scores were recorded as indicated across 28 days. The change from baseline in HAM-D total score least squares (LS) means was determined by a mixed model for repeated measures. Error bars are SE. **B.** MADRS total scores were recorded as indicated across 28 days. The change from baseline in MADRS total score least squares (LS) means was determined by a mixed model for repeated measures. Error bars are SE. **C.** HAM-A total scores were recorded as indicated across 28 days. The change from baseline in HAM-A total score least squares (LS) means was determined by a mixed model for repeated measures. Error bars are SE. n=13 per time point.

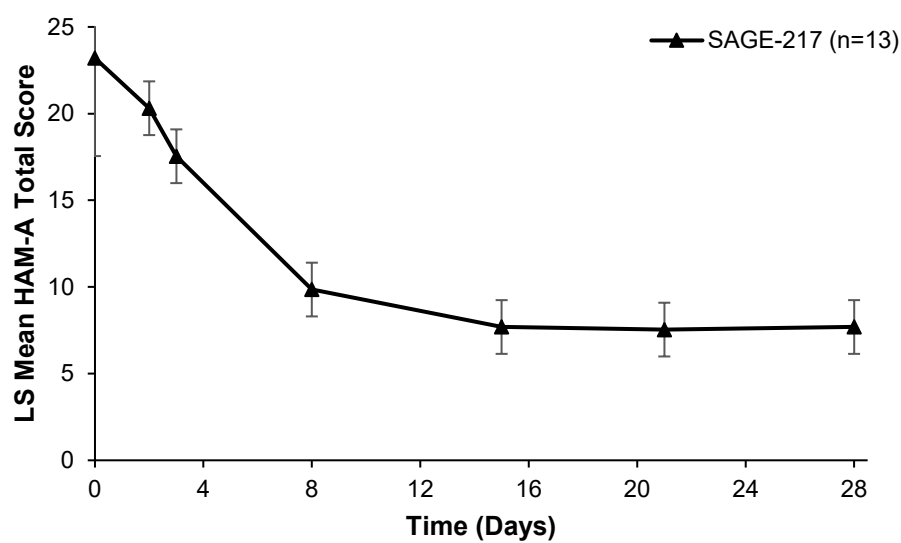
A)



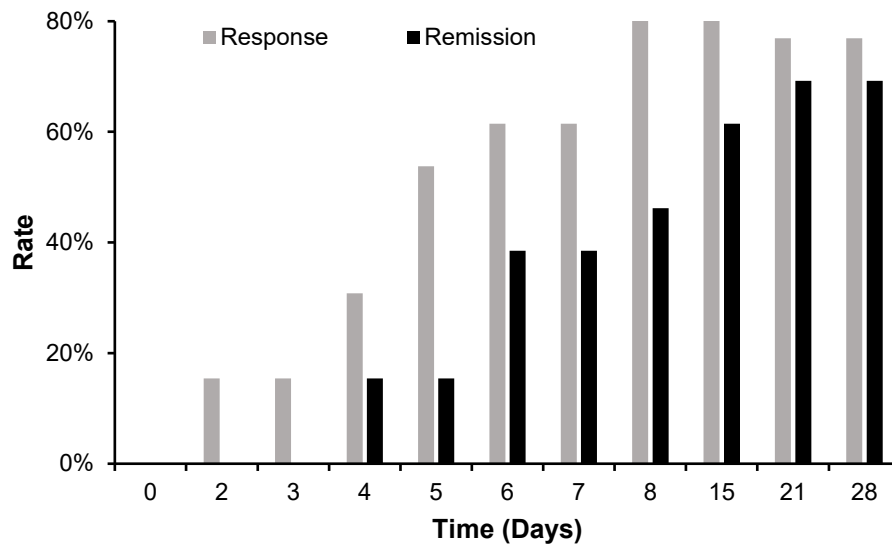
B)



C)

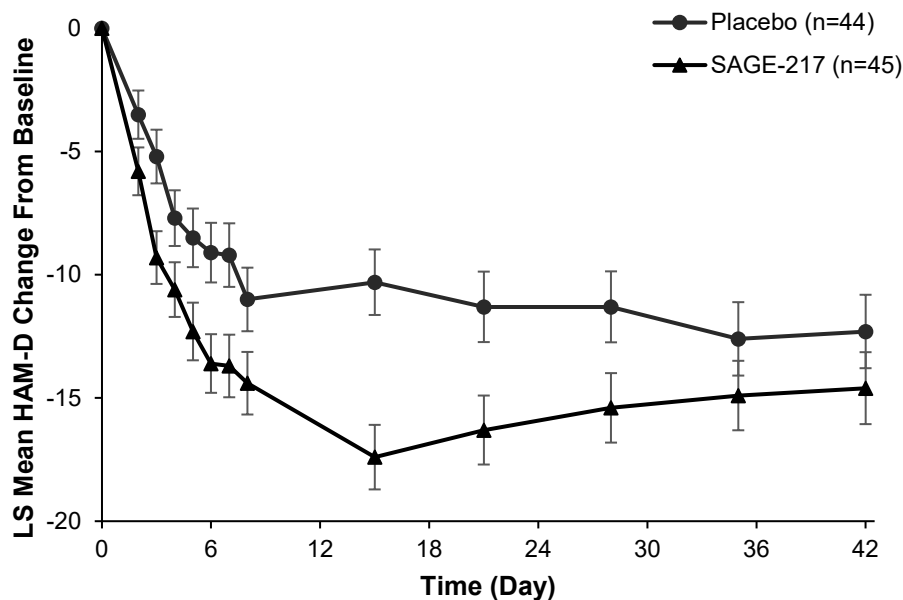


Supplemental Figure 2. HAM-D Response and HAM-D Remission Rates in the open-label study of SAGE-217 in MDD. HAM-D response was defined as a $\geq 50\%$ decrease from the baseline HAM-D total score. HAM-D remission was defined as having a HAM-D total score ≤ 7 . n=13.

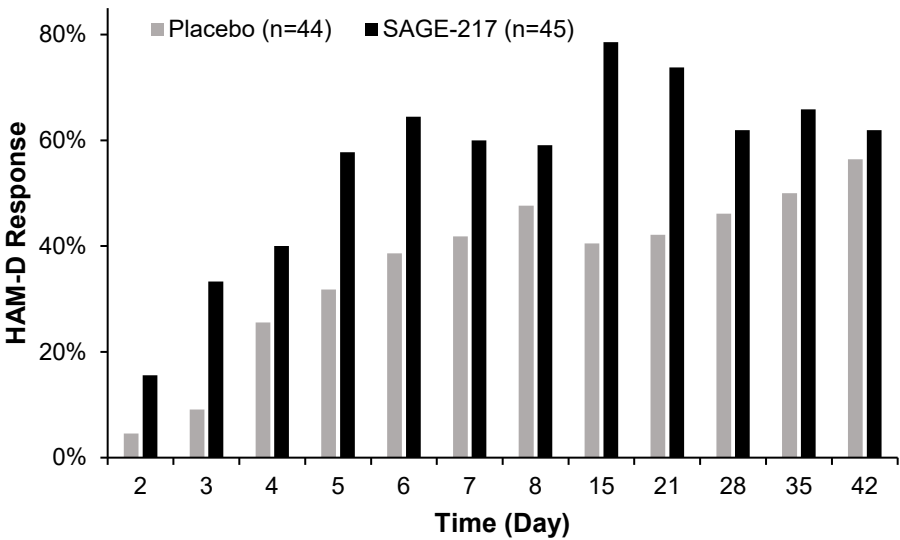


Supplemental Figure 3. HAM-D change from baseline, HAM-D response, and HAM-D remission up to Day 42 in the double-blind, randomized, placebo-controlled study. A. The change from baseline in HAM-D least squares (LS) means was determined by a mixed model for repeated measures. Error bars are SE. **B.** HAM-D response was defined as a reduction from baseline HAM-D total score of 50% or greater and was evaluated using a generalized estimating equation model. **C.** HAM-D remission was defined as a HAM-D total score of 7 or less and was evaluated using a generalized estimating equation model. SAGE-217, n=45; Placebo, n=44 for each measure.

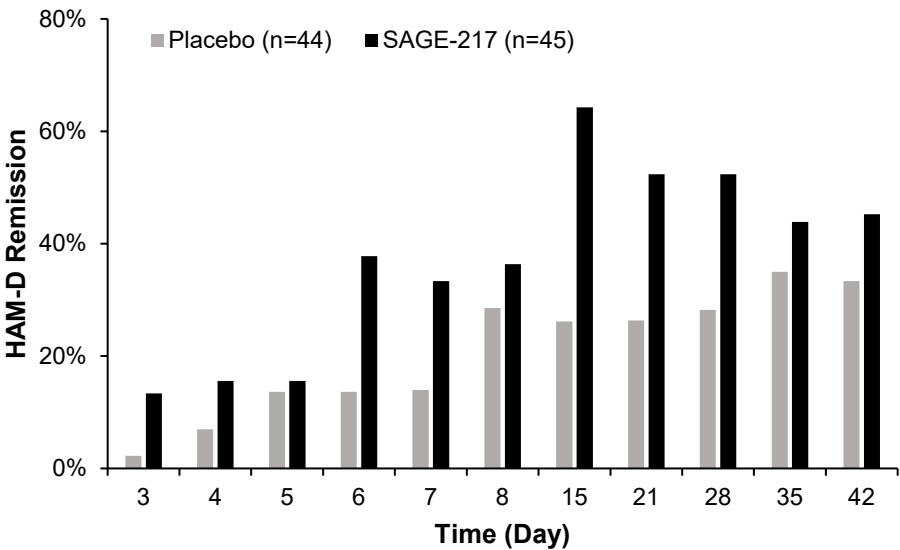
A)



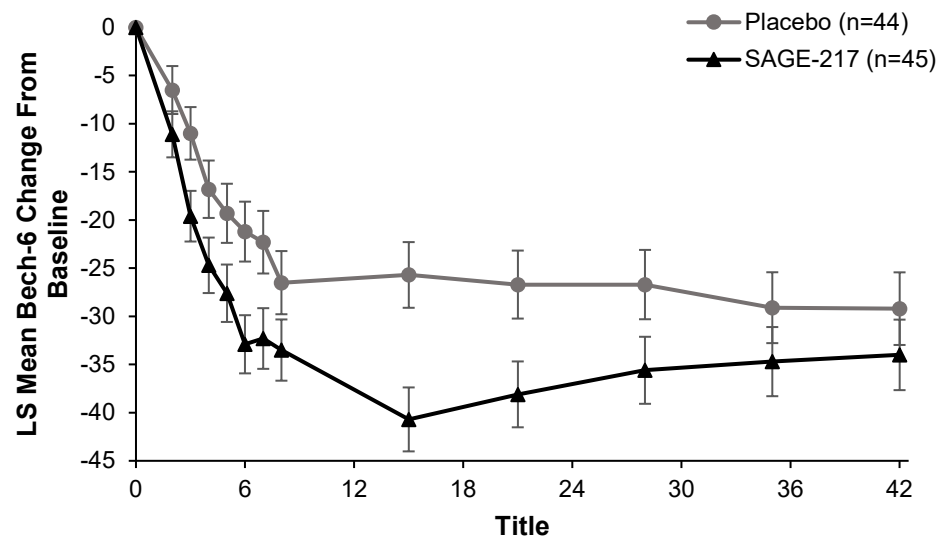
B)



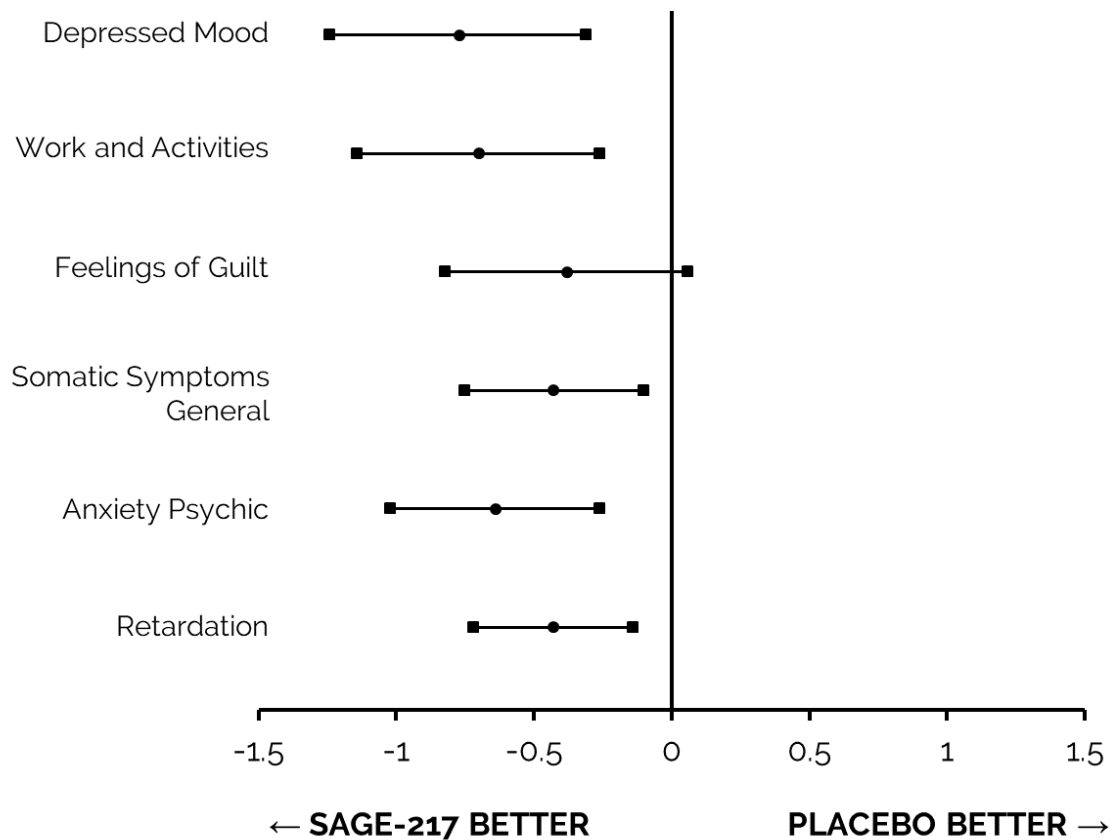
C)



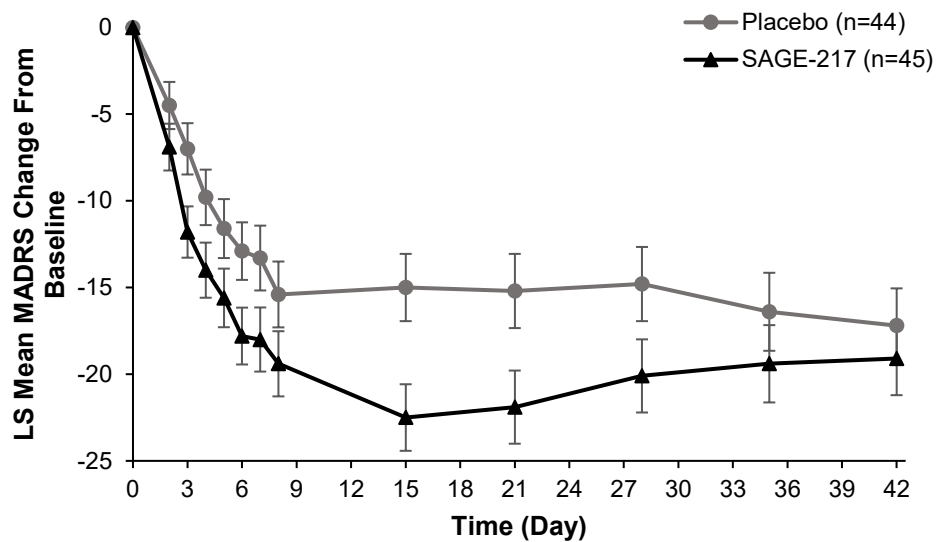
Supplemental Figure 4. Bech-6 subscale change from baseline in the double-blind, randomized, placebo-controlled study. Least squares (LS) mean Bech-6 scores were calculated at each time point using a mixed model for repeated measures. Error bars are SE. SAGE-217 (n=45); Placebo (n=44).



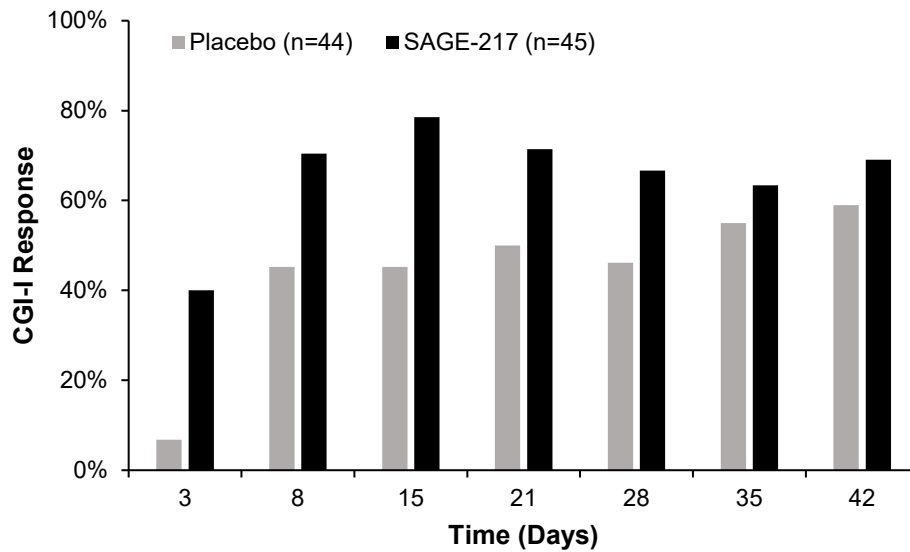
Supplemental Figure 5. Improvements in the items of the Bech-6 subscale in the double-blind, randomized, placebo-controlled study at the primary endpoint, Day 15. The individual items comprising the Bech-6 subscale of the HAM-D were analyzed by a mixed model for repeated measures. LS mean differences and 95% CIs are shown. SAGE-217, n=45; Placebo, n=44.



Supplemental Figure 6. Montgomery-Åsberg Depression Rating Scale (MADRS) change over time in the double-blind, randomized, placebo-controlled study. MADRS total scores were recorded as indicated across 42 days. The change from baseline in MADRS total score least squares (LS) means was determined by a mixed model for repeated measures. Error bars are SE. SAGE-217, n=45; Placebo, n=44.



Supplementary Figure 7. CGI-I Response in the double-blind, randomized, placebo-controlled study. CGI-I response was considered a score of 1 (very much improved) or 2 (much improved) and was analyzed using a generalized estimating equation model. SAGE-217, n=45; Placebo, n=44.



Supplemental Figure 8. HAM-A in the double-blind, randomized, placebo-controlled study. HAM-A total scores were recorded as indicated across 42 days. The change from baseline in HAM-A total score least squares (LS) means was determined by a mixed model for repeated measures. Error bars are SE. SAGE-217, n=45, Placebo, n=44.

