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Supplementary Material

Article Title: Zuranolone in Major Depressive Disorder: Results From MOUNTAIN—A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

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Disclaimer

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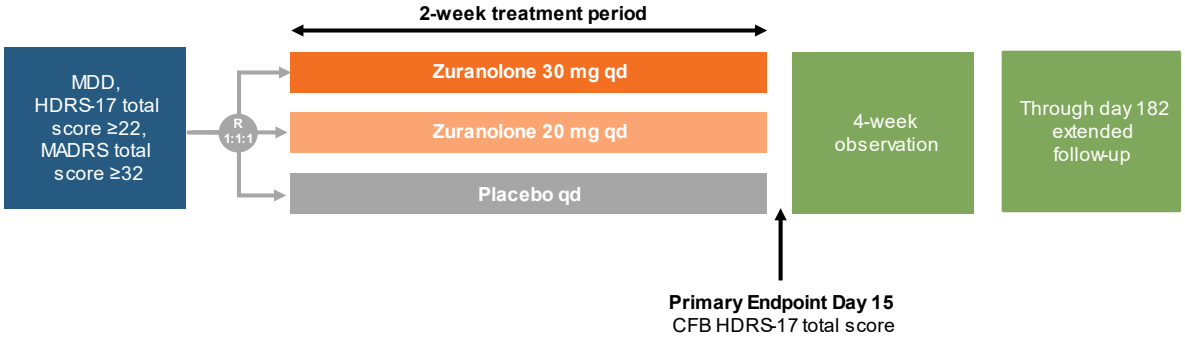
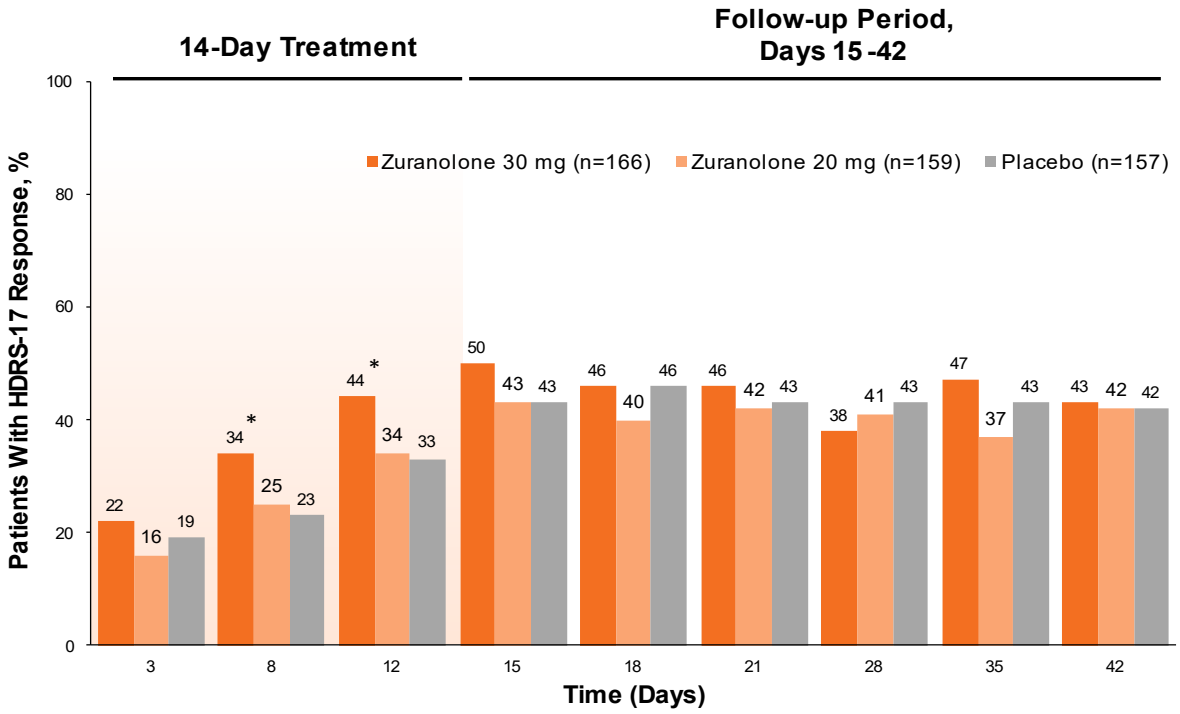
Supplementary Figure 1. Study Design



Abbreviations: HDRS-17=17-item Hamilton Depression Rating Scale total score, MADRS=Montgomery-Åsberg Depression Rating Scale total score, MDD=major depressive disorder, qd=once daily, R=randomization.

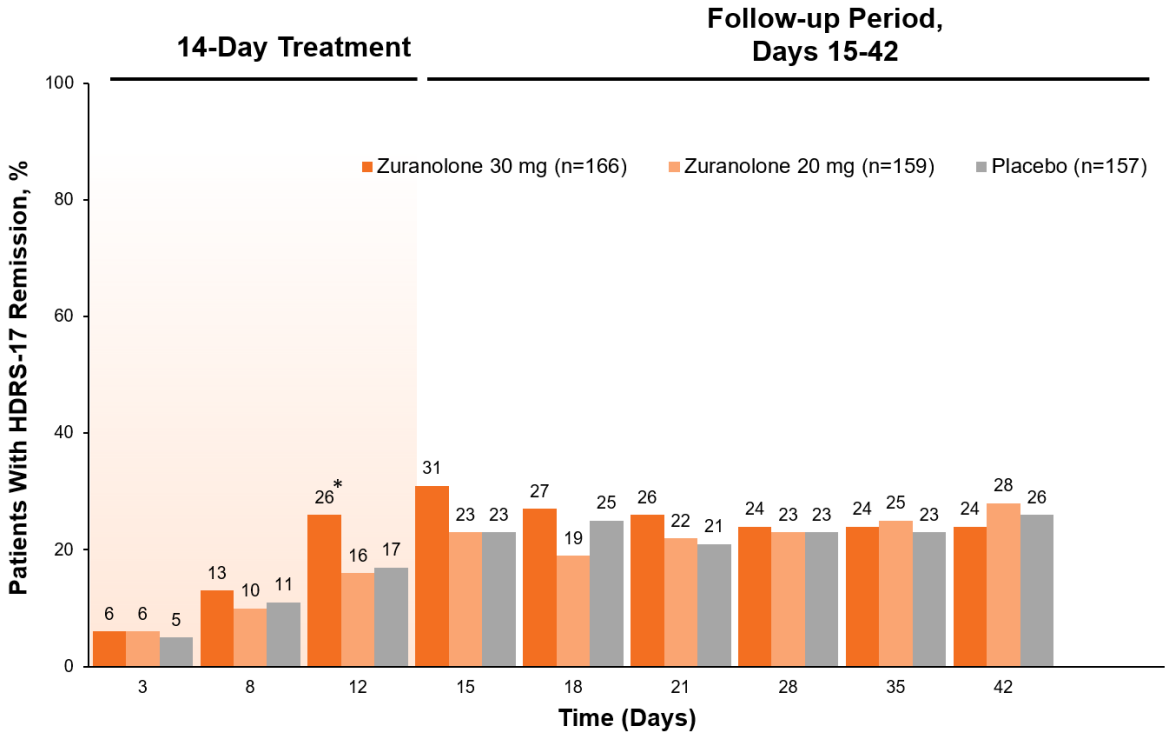
Supplementary Figure 2. Summary of HDRS-17 Response Over Time (mFAS)



Placebo n=157	152 147 141 138 146	142 141 135
Zuranolone 20 mg n=158	155 154 152 151 149	146 145 140
Zuranolone 30 mg n=163	160 154 153 149 149	149 142 136

*P<.05 vs placebo.
HDRS-17 response, ≥50% reduction from baseline in HDRS-17 total score. Secondary and post hoc analyses were not adjusted for multiplicity.
Abbreviations: HDRS-17=17-item Hamilton Depression Rating Scale total score, mFAS=modified full analysis set, n=the number of patients on that day.

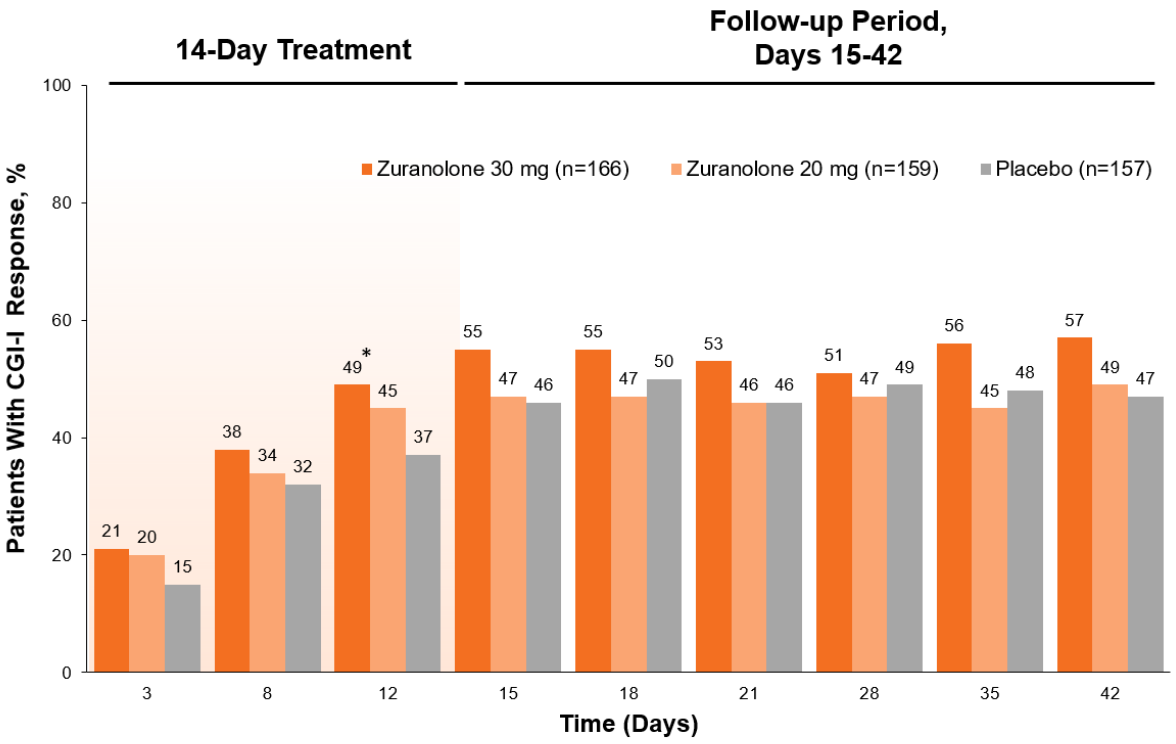
Supplementary Figure 3. Summary of HDRS-17 Remission Over Time (mFAS)



Placebo	n=157	152	147	141	138	146	142	141	135
Zuranolone 20 mg	n=158	155	154	152	151	149	146	145	140
Zuranolone 30 mg	n=163	160	154	153	149	149	149	142	136

*P<.05 vs placebo.
HDRS-17 remission, HDRS-17 total score of ≤7. Secondary and post hoc analyses were not adjusted for multiplicity.
Abbreviations: HDRS-17=17-item Hamilton Depression Rating Scale total score, mFAS=modified full analysis set, n=the number of patients on that day.

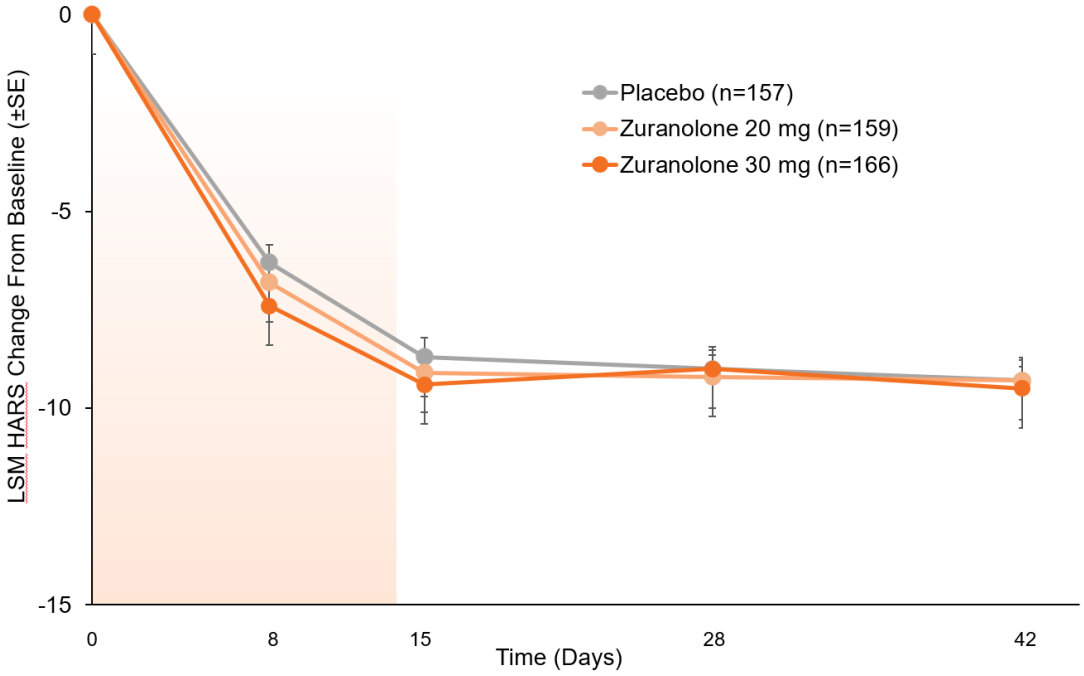
Supplementary Figure 4. Summary of CGI-I Responses Over Time (mFAS)



Placebo	n=157	152	147	141	138	146	142	141	135
Zuranolone 20 mg	n=158	155	154	151	152	149	146	145	140
Zuranolone 30 mg	n=163	160	154	152	150	149	148	142	137

*P<.05 vs placebo.
CGI-I uses a 7-point scale; a lower score indicates improvement; a score of zero denotes 'not assessed' and has been excluded. CGI-I response is defined as having a CGI-I score of "very much improved" or "much improved." The denominator of percentage is the number of patients with non-missing CGI-I score at the visit. Secondary and post hoc analyses were not adjusted for multiplicity.
Abbreviations: CGI-I=Clinical Global Impression-Improvement, mFAS=modified full analysis set, n=the number of patients on that day.

Supplementary Figure 5. LSM (±SE) Change From Baseline in HARS Over Time (mFAS)

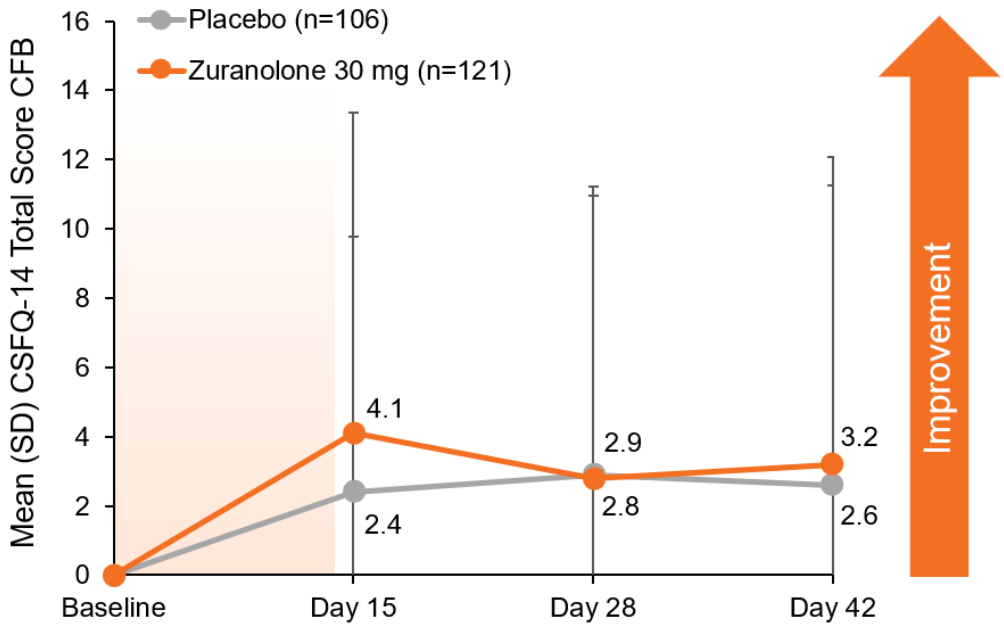


Placebo	n=157	152	141	142	135
Zuranolone 20 mg	n=159	154	151	146	140
Zuranolone 30 mg	n=166	160	153	146	137

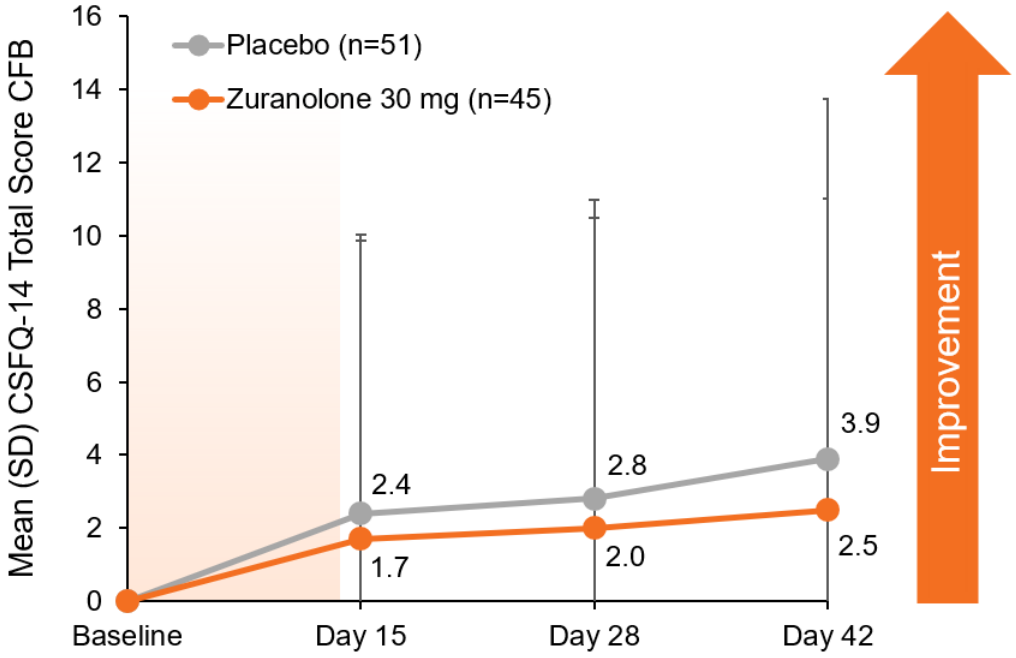
The HARS was calculated as the sum of the 14 individual item scores. A negative change indicates improvement. Model used was the mixed effects for repeated measures with treatment (zuranolone 30 mg, zuranolone 20 mg, or placebo), baseline HARS, SOC antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure. Secondary and post hoc analyses were not adjusted for multiplicity.
Abbreviations: HARS=Hamilton Anxiety Rating Scale total score, LSM=least-squares mean, mFAS=modified full analysis set, n=the number of patients on that day, SOC=standard of care.

Supplementary Figure 6. Change From Baseline in CSFQ-14 (mFAS) in A) Female and B) Male Patients.

Supplementary Figure 6A



Supplementary Figure 6B



Placebo	n=51	49	49	44
Zuranolone 30 mg	n=45	42	41	37

The CFSQ is a 14-item questionnaire measuring male and female sexual functioning. The 5 subscale scores are obtained by summing the individual items within each subscale, and the total CSFQ score is the sum of all 14 items. A higher score reflects better sexual functioning. Secondary and post hoc analyses were not adjusted for multiplicity. Abbreviations: CFB=change from baseline, CSFQ=Changes in Sexual Functioning Questionnaire short-form total score, mFAS=modified full analysis set, n=the number of patients on that day.

Supplementary Table 1. Cohen *d* estimates for HDRS-17 over time (Primary and Secondary Analyses)

Study Visit	Cohen *d* (95% CI)	
	Zuranolone 20 mg	Zuranolone 30 mg
Day 3	−0.05 (−0.27 to 0.17)	−0.28 (−0.50 to −0.06)
Day 8	−0.07 (−0.30 to 0.15)	−0.26 (−049 to −0.04)
Day 12	−0.03 (−0.25 to 0.20)	−0.26 (−0.49 to −0.03)
Day 15	−0.03 (−0.26 to 0.20)	−0.17 (−0.40 to 0.06)

Abbreviations: CI = confidence interval, HDRS-17 = 17-item Hamilton Depression Rating Scale total score.

Supplementary Table 2. Cohen *d* estimates for HDRS-17 (Post Hoc Analyses)

Subgroup	Cohen *d* (95% CI)	
	Zuranolone 20 mg	Zuranolone 30 mg
Patients with Baseline HDRS-17 ≥24	−0.06 (−0.31 to 0.20)	−0.33 (−0.59 to −0.08)
Excluding patients with post baseline BLQ in the pharmacokinetics data	−0.04 (−0.28 to 0.20)	−0.23 (−0.47 to 0.00)
Patients with Baseline HDRS-17 ≥24 excluding those with post baseline BLQ in the pharmacokinetics data	−0.04 (−0.31 to 0.24)	−0.32 (−0.60 to −0.05)

Abbreviations: BLQ = below limit of quantification, CI = confidence interval, HDRS-17 = 17-item Hamilton Depression Rating Scale total score.

Appendix 1

List and Description of Investigators and Other Important Participants in the Study

Study Sites	
Midwest Clinical Research Center Dayton, OH 45417	California Neuroscience Research Medical Group, Inc. Sherman Oaks, CA 91403
Atlanta Center for Medical Research Atlanta, GA 30331	St. Louis Clinical Trials, LC St. Louis, MO 63141 Replaced: St. Louis Clinical Trials, LC St. Louis, MO 63141 Replaced: St. Louis Clinical Trials, LC St. Louis, MO 63141
Behavioral Research Specialists, LLC Glendale, CA 91206	Patient Priority Clinical Sites, LLC Cincinnati, OH 45215
Sooner Clinical Research Oklahoma City, OK 73112	NRC Research Institute Orange, CA 92868
Oregon Center for Clinical Investigations, Inc. Portland, OR 97214	Woodland Research Northwest, LLC Rogers, AR 72758 Replaced: Woodland Research Northwest, LLC Rogers, AR 72758
CITrials Bellflower, CA 90706	InSite Clinical Research, LLC DeSoto, TX 75115
Synexus Clinical Research US, Inc. Jamaica, NY 11432	Altea Research Institute Las Vegas, NV 89102
CNS Clinical Research Group Coral Springs FL, 33067	IPS Research Company Oklahoma City, OK 73103 Location Change: IPS Research Company Oklahoma City, OK 73106
Combined Research Orlando Phase I-IV Orlando, FL 32807	Psychiatric Care and Research Center O'Fallon, MO 63368

Study Sites	
Anderson Clinical Research Redlands, CA 92374	Precise Research Centers Flowood, MS 39232
Carolina Clinical Trials, Inc. Charleston, SC 29407	Finger Lakes Clinical Research Rochester, NY 14618
Behavioral Clinical Research, Inc. North Miami, FL 33161	SW Biomedical Research, LLC Tucson, AZ 85712
Summit Research Network (Oregon) Inc. Portland, OR 97210	New Hope Clinical Research Charlotte, NC 28211
Collaborative Neuroscience Network, LLC Garden Grove, CA 92845	Research Strategies of Memphis, LLC Memphis, TN 38119 Location Change: Research Strategies of Memphis, LLC Memphis, TN 38119
Lehigh Center for Clinical Research Allentown, PA 18104	Medical Research Group of Central Florida Orange City, FL 32763
California Neuropsychopharmacology Clinical Research Institute – LA, LLC Pico Rivera, CA 90660	Research Centers of America, LLC Hollywood, FL 33024
Clinical Neuroscience Solutions, Inc. Jacksonville, FL 32256	Neuro-Behavioral Clinical Research, Inc. Canton, OH 44718
Community Clinical Research, Inc Austin, TX 78754	iResearch Atlanta, LLC Decatur, GA 30030 Location Change: iResearch Atlanta, LLC Decatur, GA 30030
UVA Center for Psychiatric Clinical Research Charlottesville, VA 22903	Houston Clinical Trials, LLC Bellaire, TX 77401
BTC of Lincoln, LLC Lincoln, RI 02865	Grayline Research Center Wichita Falls, TX 76309
Pharmasite Research Baltimore, MD 21208	Institute for Advanced Medical Research at Mercer University Atlanta, GA 30341 Institute for Advanced Medical Research at Mercer University Alpharetta, GA 30022

Study Sites	
Innovative Clinical Research, Inc. Lauderhill, FL 33319	Pillar Clinical Research, LLC Richardson, TX 75080
Synexus Clinical Research US, Inc. Atlanta, GA 30328	Hassman Research Institute Berlin, NJ 08009 Hassman Research Institute Marlton, NJ 08053
North County Clinical Research Oceanside, CA 92054	Synergy San Diego Lemon Grove, CA 91945
Clinical Neuroscience Solutions, Inc. Memphis, TN 38119	Artemis Institute for Clinical Research San Diego, CA 92103 Replaced: Artemis Institute for Clinical Research San Diego, CA 92103
Pacific Research Partners, LLC Oakland, CA 94607	Clinical Neuroscience Solutions, Inc Orlando, FL 32801
Viking Clinical Research Temecula, CA 92591	Meridien Research Maitland FL 32751
Psychiatric Medicine Associates, LLC Skokie IL, 60076	

Appendix 2

Study Inclusion/Exclusion Criteria

Inclusion Criteria

1. Patient had signed an Informed Consent Form prior to any study-specific procedures being performed.
2. Patient was a male or female between 18 and 64 years of age, inclusive.
3. Patient was in good physical health and had no clinically significant findings, as determined by the investigator, on physical examination, 12-lead electrocardiogram (ECG), or clinical laboratory tests.
4. Patient agreed to adhere to the study requirements, including to not participate in night-shift work.
5. Patient had received a diagnosis of major depressive disorder (MDD) as assessed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trial Version (SCID-5-CT), with symptoms that had been present for at least a 4-week period.
6. Patient had a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥32 and a HDRS-17 ≥22 at screening and day 1 (prior to dosing).
7. Patients who were taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to day 1. Patients who stopped taking antidepressants within 60 days must have stopped for longer than 5 half-lives of the antidepressant prior to day 1. Patients who received psychotherapy must have received therapy on a regular schedule for at least 60 days prior to day 1.
8. Patient was willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, until after completion of the day 42 visit.
9. Female patient agreed to use one of the following methods of contraception during the treatment period and for 30 days following the last dose of study drug, unless she was postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy), or had not engaged in sexual relations that carried a risk of pregnancy:
    - 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 ligation/occlusion.
    - Vasectomized partner.
10. Male patient agreed to use an acceptable method of effective contraception during the treatment period and for 5 days after receiving the last dose of the study drug, unless the patient did not engage in sexual relations that carried a

risk of pregnancy. Acceptable methods of effective contraception for males included vasectomy, or a condom with or without spermicide used together with highly effective female contraception methods if the female partner was of child-bearing potential (see Inclusion Criterion #9 for acceptable contraception methods).

11. Male patient was willing to abstain from sperm donation during the treatment period and for 5 days after receiving the last dose of the study drug.
12. Patient agreed to refrain from using drugs of abuse and alcohol for the duration of the study.

Exclusion Criteria

1. Patient was currently at significant risk of suicide, as judged by the investigator, or had attempted suicide associated with the current episode of MDD.
2. Patient had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the patient had presented for screening during the 6-month postpartum period.
3. Patient had 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 patient's ability to complete or participate in this clinical study. A BMI ≤18 or ≥50 kg/m^2 at screening was exclusionary; a BMI of 40 to 49 kg/m^2, inclusive, at screening was subject to a broader evaluation of medical co-morbidities (such as sleep apnea, chronic obstructive pulmonary disease [COPD]), concomitant medications, and prior tolerability of sedating agents.
4. Patient had treatment-resistant depression (TRD), defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from 2 different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) was used for this purpose to evaluate patients for TRD.
5. Patient had vagus nerve stimulation, electroconvulsive therapy, or had taken ketamine within the current major depressive episode.
6. Patient had a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Patient had a positive pregnancy test at screening or on day 1 prior to the start of study drug administration or, if she was breastfeeding at screening or on day 1 (prior to administration of study drug), she agreed to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on day 1 until 7 days after the last dose of study drug.
8. Patient had detectable hepatitis B surface antigen, anti-hepatitis C virus, and positive hepatitis C virus viral load, or HIV antibody at screening.
9. Patient had a clinically significant abnormal 12-lead ECG at the screening or baseline visits. NOTE: mean QT corrected according to Fridericia's formula

(QTcF) of >450 msec in male participants or >470 msec in female participants was the basis for exclusion from the study.
10. Patient had active psychosis per investigator assessment.
11. Patient had a medical history of seizures.
12. Patient had a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Patient had a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria in the 12 months prior to screening.
14. Patient had exposure to another investigational medication or device within 30 days prior to screening.
15. Patient had previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical study.
16. Patient had used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever was longer) or had consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to the first dose of Investigational Product (IP).
17. Patient had used any strong CYP3A inducer, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort within 28 days prior to the first dose of IP.
18. Patient had a positive drug and/or alcohol screen at screening or on day 1 prior to dosing.
19. Patient planned to undergo elective surgery before completion of the day 42 visit.
20. Patient was taking benzodiazepines, barbiturates, or $GABA_A$ receptor modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at day −28 or had been using these agents daily or near-daily (≥4 times per week) for >1 year. Patient was taking any benzodiazepine or GABA modulator with a half-life ≥48 hours (eg, diazepam) from within 60 days prior to day 1.
21. Patient was taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [antihistamine], trazodone), or first- or second-generation (typical/atypical) antipsychotics at day −14.
22. Patient had been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma *in situ*) within the year prior to screening.
23. Patient had a history of sleep apnea.
24. Patient had gastric bypass surgery, a gastric sleeve or lap band, or any related procedures that interfere with gastrointestinal transit.
25. Patient had taken psychostimulants (eg, methylphenidate, amphetamine) or opioids, regularly or as needed, at day −28.

Appendix 3

Statistical Analysis Plan

Determination of Sample Size

Assuming a two-sided alpha level of 0.05, a sample size of 399 evaluable patients would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint and change from baseline in 17-item Hamilton Depression Rating Scale total score (HDRS-17) at day 15, assuming a standard deviation (SD) of 10 points. Assuming an 11% dropout rate and a 1:1:1 randomization ratio within each stratum (antidepressant use at baseline, Yes or No), approximately 450 total randomized patients will be required to obtain 399 evaluable patients. Evaluable patients are defined as those randomized patients who receive study drug and have valid baseline and at least 1 post-baseline HDRS-17 assessment. Additional patients may be randomized if the dropout rate is greater than 11%.

Emergency Identification of Study Drug

During the study, the blind is to be broken only when the safety of a patient is at risk and the treatment plan is dependent on the study treatment received. Unless a patient is at immediate risk, the Investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a patient. Requests from the Investigator about the treatment administered to study patients should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

Randomization and Sampling

This is a randomized double-blind, placebo-controlled trial. For both study parts, patients who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline.

Randomization will be done within each stratum in a 1:1:1 ratio to receive SAGE-217 20 mg, SAGE-217 30 mg, or matched placebo.

In both study parts, patients, clinicians, and the study team will be blinded to treatment allocation. Randomization will be performed centrally via an interactive response technology system. An independent statistician will generate randomization schedules. The allocation to treatment group will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding.

The Sponsor will be unblinded following the first database lock when all patients complete the day 42 visit; site personnel and patients will remain blinded throughout the extended follow-up until the final database lock when all patients complete the day 182 visit.

Appendix 4

Patient Narrative

Patient was a 57-year-old male, White (not Hispanic or Latino) with a body mass index (BMI) of 39.8 kg/m^2 (weight 117.7 kg, height 172 cm). His first depressive episode was in 2015. At enrollment into the study, this was his second depressive episode with the current episode beginning in February 2018, more than 1 year before zuranolone was initiated. He reported no family history of psychiatric conditions. In addition to MDD, the participant's concurrent medical conditions included back pain, chronic obstructive pulmonary disease (COPD), and hypertension. Concomitant medications included citalopram once daily for MDD, acetylsalicylic acid as needed for lower back pain, salbutamol once daily for COPD, and lisinopril once daily for hypertension.

The participant completed 14 days of dosing with zuranolone. The site reported that because the participant did not present for the visit on day 183 (January 20, 2020), his emergency contact was reached, who indicated that he had passed away on day 142 (December 10, 2019). The only information provided was that on day 142, the participant had not woken up; emergency medical service was called to the scene, and he was pronounced dead because of unknown reasons. No further information regarding cause of death was available. The participant visited the clinic on day 126; all vitals were normal and there were no adverse events reported. The investigator and sponsor both assessed the death as not related to the zuranolone.