Document Type: Protocol

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial of AXS-05 in Subjects with Major Depressive Disorder

ClinicalTrials.gov Identifier: NCT04019704

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Certain information within this protocol has been redacted to protect either personally identifiable information (PII) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information.
- Other information as needed to protect the confidentiality of Axsome Therapeutics, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

COMPOUND NAME/NUMBER:	AXS-05
PROTOCOL NUMBER:	AXS-05-MDD-301
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	A Randomized, Double-Blind, Placebo-Controlled Trial of AXS-05 in Subjects with Major Depressive Disorder
PROTOCOL VERSION:	Original / 12May2019

AXSOME
THERAPEUTICS

[redacted]

APPROVAL SIGNATURES

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PROTOCOL VERSION: Original / 12May2019

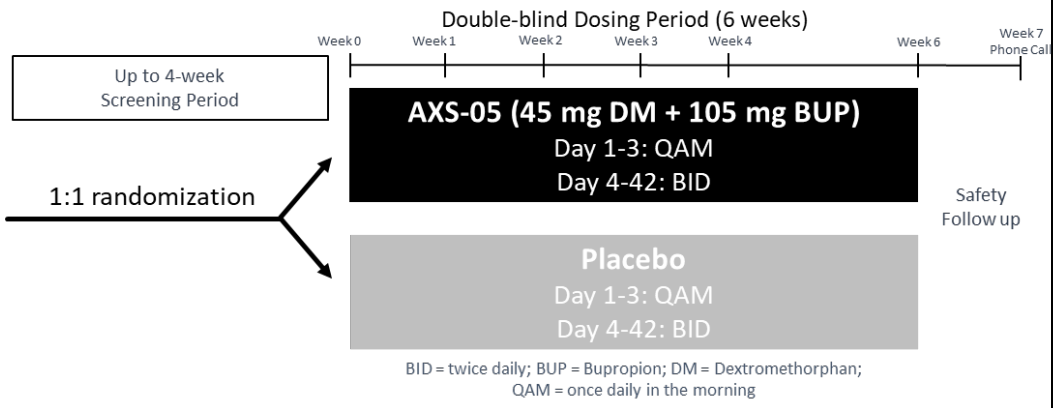
I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Study Contact and Details

SPONSORED BY:	Axsome Therapeutics, Inc.
[redacted]	[redacted]
[redacted]	[redacted]
INVESTIGATORS:	Multi-Center

1. SYNOPSIS

CLINICAL STUDY SYNOPSIS: AXS-05-MDD-301	
Product Name/ Number	AXS-05 (bupropion hydrochloride and dextromethorphan hydrobromide monohydrate)
Protocol Number	AXS-05-MDD-301
Protocol Title	A Randomized, Double-Blind, Placebo-Controlled Trial of AXS-05 in Subjects with Major Depressive Disorder
Indication	Treatment of Major Depressive Disorder (MDD)
Development Phase	3
Objective	To evaluate the safety of AXS-05 in subjects with MDD
Study Design	This study is a randomized, double-blind, placebo-controlled, Phase 3 trial, consisting of a screening period of up to 4 weeks, a 6-week treatment period and a 1-week safety follow up period. **Screening Period** Prior to randomization, all subjects will enter an up to four-week screening period (Screening) to determine eligibility. Eligible subjects must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features, based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version (SCID-5-CT), with a current major depressive episode of at least 4 weeks in duration. Eligible subjects must meet all other inclusion and no exclusion criteria. **Treatment Period** Randomization Subjects who successfully complete Screening will be randomly assigned at the baseline visit (Baseline) to receive either AXS-05 or placebo in a 1:1 ratio for 6 weeks. The randomization schedule will be computer-generated using a permuted block algorithm that will randomly allocate the study drug to randomization numbers. Treatments Doses will be titrated as follows: • Days 1 - 3 o AXS-05 group: AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet once daily (QD) o Placebo group: Placebo tablet QD • Days 4 - 42 o AXS-05 group: AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet twice daily (BID) o Placebo group: Placebo tablet BID All QD doses will be taken in the morning, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All BID doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All study drug is of identical appearance and similar weight in order to maintain the integrity of the blind. **Assessments and Visits** Study visits will occur at Screening (Visit 1), Baseline (Day1, Visit 2), and on Days 4, 8, 15, 22, 29, 43 and 50 (Visits 3 – 9). Study procedures and assessments will be performed during study visits as outlined in the Schedule of Assessments. Visit 3 (Day 4) will be conducted telephonically. Subjects will be reminded during Visit 3 to begin BID dosing on Day 4. A one-week safety follow-up visit (Visit 9) will occur telephonically. Subjects who prematurely discontinue the study will be encouraged to complete Visit 9.

	Assessments will include safety parameters, MADRS, SDS, Q-LES-Q-SF, QIDS-SR-16, CGI-S, CGI-I and PGI-I. [redacted] Study drug compliance will also be assessed at the 80-120% level by counting the number of tablets dispensed and returned. Noncompliant subjects are subject to early termination from the study. **AXS-05-MDD-301 Study Design** 
Planned Number of Subjects	Approximately 300 subjects will be randomized.
Study Centers	Up to approximately 50 U.S. study centers.
Diagnosis and Subject Selection Criteria **-Inclusion Criteria** **-Exclusion Criteria**	**Inclusion Criteria**: 1. Provides written informed consent to participate in the study, is able to understand the procedures and study requirements, and agrees to abide by the study restrictions and return for the required study assessments. 2. Male or female outpatients, 18 to 65 years of age, inclusive. 3. Currently meets the DSM-5 criteria for MDD without psychotic features, based on the SCID-5-CT, with a current major depressive episode of at least 4 weeks in duration at Visit 1. 4. MADRS score of ≥ 25 and CGI-S ≥ 4 at Screening (Visit 1) and Baseline (Visit 2). 5. Normal physical examination findings and clinical laboratory test results from Screening (Visit 1) or abnormal results that are judged not clinically significant by the investigator. 6. Body mass index (BMI) between 18 and 40 kg/m^2, inclusive. 7. If female and of childbearing potential, has a negative urine pregnancy test result at Visit 1 and Visit 2, is practicing at least two adequate methods of birth control (i.e., oral or parenteral contraceptives, intrauterine device, condoms, spermicides), and is not currently pregnant or breastfeeding nor plans to become pregnant during the course of the study. a. Long-term abstinence is acceptable when it is in line with the subjects preferred and usual lifestyle. b. Female subjects using a hormonal contraceptive or intrauterine device must have been doing so for at least 1 month before Screening and must follow that product's package insert instructions including additional protection at times when hormonal contraceptive doses might be missed.

c. Female subjects may be enrolled without a negative urine pregnancy test if they are surgically sterile or at least 2 years post-menopausal.
d. Male subjects and their female sexual partners should use an acceptable method of birth control (as noted above) during the study.

Exclusion Criteria:

Psychiatric Criteria:

1. History of:
   a. Any depressive episode with psychotic or catatonic features
   b. Any manic, hypomanic or mixed episode, including bipolar disorder (Type 1 or Type 2) and substance-induced (e.g. antidepressant-induced) manic, hypomanic/mixed episode
   c. Bipolar Depression
   d. Schizophrenia, schizoaffective, or other psychotic disorder
   e. Panic disorder, with or without agoraphobia
   f. Obsessive-compulsive disorder
   g. Bulimia or anorexia nervosa
   h. Any persistent neurocognitive disorder
   i. Any other anxiety disorder which has been the primary focus of clinical attention for the six months prior to Screening, while MDD was a secondary focus of attention
2. History of treatment resistant depression defined as 2 or more failed treatments of adequate dose and duration in the current depressive episode.
3. Improvement in MADRS score of ≥ 25% between Visit 1 and Visit 2.
4. Post-traumatic stress disorder, active within 3 years of Visit 1.
5. Borderline or antisocial personality disorder or other disorder of sufficient severity to interfere with participation in this study.
6. Alcohol/substance use disorder (other than nicotine or caffeine), active within 1 year of Visit 1.
7. Psychiatric hospitalization within current depressive episode.

Psychiatric symptoms secondary to any other general medical condition.

8. Clinically significant risk of suicide or harm to self or others. Risk of suicide is determined by meeting any of the following criteria:
   a. In the judgment of the investigator, the subject may be a significant risk for suicide as judged by the psychiatric interview or information collected in the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1 or Visit 2 (e.g., The subject responded "yes" to question 4 or question 5 on the screening C-SSRS, and the most recent episode occurred within the current depressive episode).
   b. The subject has attempted suicide within the current depressive episode.
   c. MADRS Item 10 score ≥ 5 at Visit 1 or Visit 2.

Treatment-Related Criteria:

9. Use of drugs that are strong inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, quinidine) as defined in FDA's Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.
10. Use of drugs that are inhibitors of CYP2B6, the primary enzyme that metabolizes bupropion (e.g. clopidogrel, ticlopidene, prasugrel), or that are inducers of CYP2B6 (e.g. ritonavir, lopinavir, efavirenz). Please refer to the Wellbutrin SR (bupropion) FDA package insert.
11. Current use, or use within 14 days before Visit 1, of monoamine oxidase inhibitors (MAOIs), or linezolid, or intravenous methylene blue.

	12. Use of opioids (e.g., codeine, oxycodone, morphine) within 14 days before Visit 1. 13. Having received any prohibited medications, supplements or herbal products [redacted] including any antipsychotic, anticonvulsant/mood stabilizer, anxiolytic, benzodiazepine, ADT, or ADT augmentation agent (e.g., T3 [except as treatment for thyroid condition], 2nd antidepressant, etc.) within 1 week or 5 half- lives of the medication, whichever is longer, prior to Visit 2; however, 4 weeks is required for T3, 2 weeks is required for MAOIs. Lithium must be tapered and followed by a 1-week washout. The safe withdrawal from benzodiazepine treatment should be decided by the patient's treating clinician and also monitored by the principal investigator. 14. History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1 (whichever is longer). 15. Requiring concomitant treatment with any of the prohibited medications, supplements, or herbal products [redacted] including any psychotropic drug or any drug with psychotropic activity or with a potentially psychotropic component, except for the following: a. Eszopiclone, zolpidem, zolpidem extended-release, zopiclone or zaleplon for insomnia may be continued provided the medication has been used in a consistent manner for 4 weeks prior to enrollment and at doses that do not exceed the maximum labeled amounts. 16. Initiation or termination of psychotherapy for depression within 3 months of Visit 1, or plans to initiate, terminate, or change such therapy during the course of the study (Support meetings or counseling [e.g., marital counseling] are allowed provided they are no more frequent than weekly and do not have treatment of depression as their objective). 17. Ongoing, initiation or termination of phototherapy within 1 month of Visit 1. ***Other Medical Criteria:*** 18. History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs; or any other condition that increases the risk of seizure such as stroke, significant head injury, tumor or infection of the central nervous system, arteriovenous malformation, neuroleptic malignant syndrome/serotonin syndrome, or clinically significant, as deemed by the investigator, metabolic disorders (e.g., clinically significant hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia). 19. Positive serum ethanol test or urine drug screen (UDS) for any prohibited medication or drugs of abuse (cocaine, marijuana, PCP, opioid or other agent that in the opinion of the investigator is being abused) at Visit 1. Subjects should be advised not to drink alcohol for at least 8 hours prior to screening labs. 20. Any current or recent medical, psychiatric, or social condition that, in the investigator's opinion, is likely to interfere with the conduct of the study, confounds the interpretation of study results, or endangers the subject's well-being. This includes (but is not limited to) any clinically significant oncologic, hematologic, endocrine/metabolic, cardiovascular, respiratory, renal, hepatic, gastrointestinal, infectious or neurologic disease or has a chronic disease which is unstable or progressive. 21. Hypertension defined as resting, sitting systolic blood pressure (BP) ≥150 mm Hg or diastolic blood pressure ≥ 95 mm Hg. Patients with high BP (as defined above) may be accepted in the study if they subsequently have acceptable BP values on reassessment at least 30 minutes apart. 22. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month before Visit 1 (Serum TSH must be > 0.75 × the LLN and < 1.25 × ULN). 23. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g. codeine, etc.), or any other ingredient in the study medication. 24. History of intolerance to bupropion or dextromethorphan.

	25. Patients who have received dextromethorphan co-administered with quinidine (e.g. Nuedexta®) within the past four weeks. 26. Gastric bypass or any condition that would be expected to affect drug absorption (lap band procedures are acceptable if there is no problem with absorption). 27. Narrow-angle glaucoma without a patent iridectomy. 28. Known human immunodeficiency virus (HIV) infection. 29. Clinically significant signs of active hepatitis B and/or C infection. 30. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase and/or alanine aminotransferase) results > 2.0 x ULN. 31. Any clinically significant abnormality on the screening laboratory tests, as assessed by the study investigator and/or the medical monitor. 32. Previously participated in another clinical study of AXS-05 or received any investigational drug or device treatment within 30 days of Visit 1. 33. Currently hospitalized or residing in an in-patient facility during the study. 34. Unable or unlikely to comply with the study protocol or unsuitable for any other reason, including other conditions that might indicate that the subject is unsuitable for the study as judged by the investigator such as known history of poor medication compliance or significant instability in status of psychosocial issues.
Test Product, Dosage, and Mode of Administration	AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet, oral
Reference Therapies, Dosage, and Mode of Administration	Placebo to match AXS-05
Treatment Regimen	Days 1 - 3 • AXS-05 group: AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet QD • Placebo group: Placebo tablet QD Days 4 - 42 • AXS-05 group: AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet BID • Placebo group: Placebo tablet BID All QD doses will be taken in the morning, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All BID doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water.
Study Duration	Up to 11 weeks: up to 4 weeks screening, followed by 6 weeks of treatment, followed by a 1-week follow-up visit.
Criteria for Evaluation	Safety assessments will include: • Adverse Event (AE) recording • Adverse Dropouts (ADOs) • Incidence of Treatment Emergent Adverse Events (TEAEs) • Clinical laboratory test results • Vital sign measurements • Physical examinations • Electrocardiogram readings • Columbia - Suicide Severity Rating Scale (C-SSRS)
Statistical Methods	**Analysis Populations:** The following analysis populations are planned for this study: ▪ *Modified Intent-to-Treat (mITT) Population*—the mITT will consist of all subjects who are randomized, take at least 1 dose of the study drug, and have at least 1 post-Baseline assessment.

	▪ *Safety Population*—the Safety Population will be the primary safety analysis population and will include all subjects who receive at least 1 dose of the study drug. All analyses, including safety analyses, will be detailed in the statistical analysis plan.
Sample Size Determination	Approximately 300 subjects (150 per arm) are planned for this study. The sample was determined based on prior reported experience with trials of a similar stage, in a similar patient population, with a similar objective.