Document Type: Protocol

Protocol Title: An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Major Depressive Disorder

ClinicalTrials.gov Identifier: NCT04039022

Document Date: July 9, 2020

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-05-303
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Major Depressive Disorder
PROTOCOL VERSION:	Amendment 3
PROTOCOL DATE:	July 9, 2020

AXSOME
THERAPEUTICS

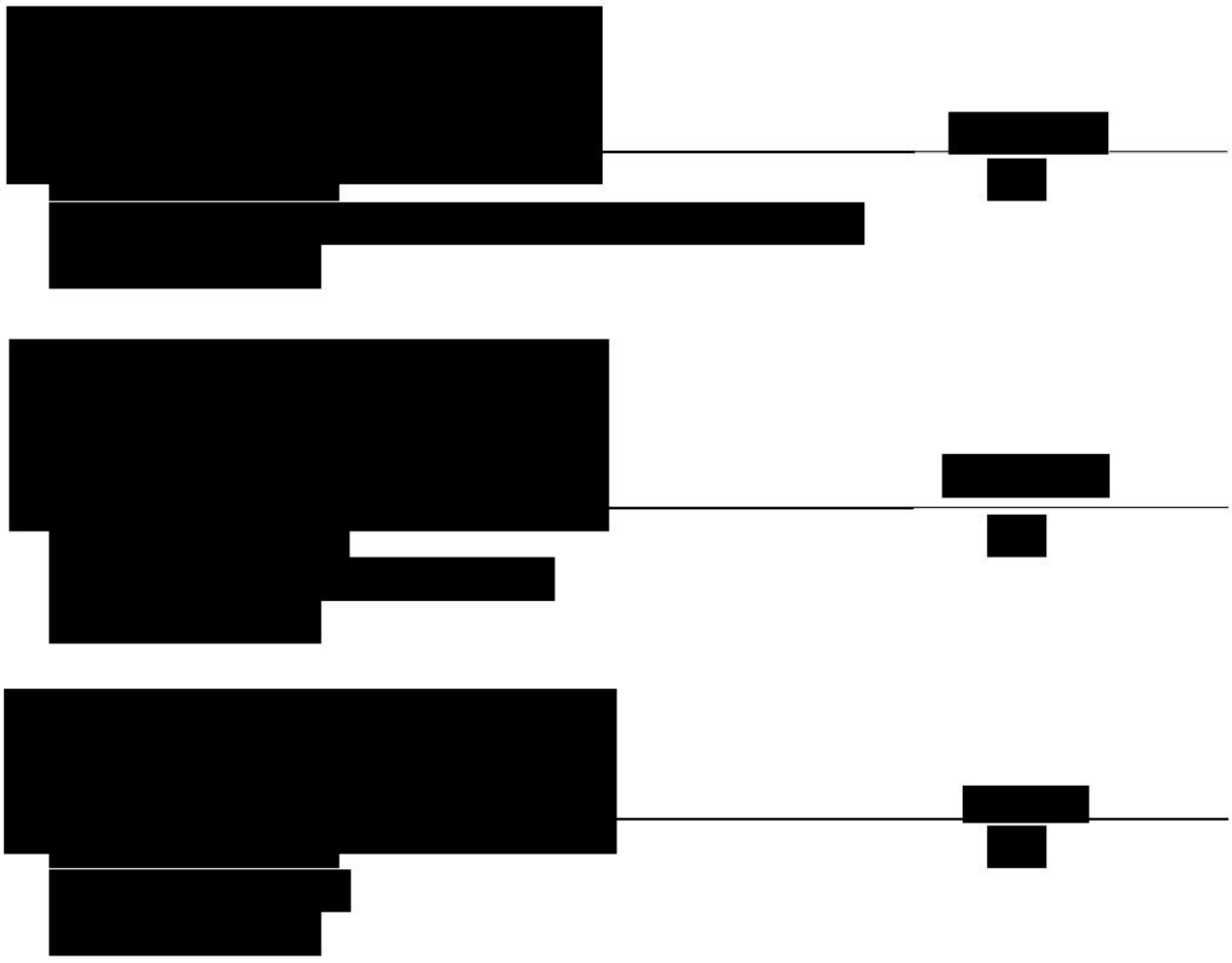
[redacted]

This study will be performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Axsome Therapeutics, Inc.

APPROVAL SIGNATURES

PROTOCOL NUMBER:	AXS-05-303
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Major Depressive Disorder
Protocol Version:	Amendment 3: July 9, 2020

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]
[redacted]	[redacted]
[redacted]	[redacted]
INVESTIGATORS:	A current list of clinical investigators will be maintained in the Trial Master File (TMF)

1. SYNOPSIS

Product Name/ Number	AXS-05 (bupropion hydrochloride and dextromethorphan hydrobromide monohydrate)
Protocol Number	AXS-05-303
Protocol Title	An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Major Depressive Disorder
Indication	Treatment of Major Depressive Disorder (MDD)
Development Phase	3
Objective	The primary objective of this study is to evaluate the long-term safety and efficacy of AXS-05 for the treatment of MDD.
Study Design	This study is a multi-center, open-label trial to evaluate the long-term safety and efficacy of AXS-05 in subjects with major depressive disorder (MDD). Eligible subjects must have completed a prior MDD study with AXS-05 (AXS-05-301 or AXS-05-MDD-301) immediately prior to enrollment in this study or meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features. Subjects who meet the eligibility criteria will receive AXS-05 (105 mg bupropion / 45 mg dextromethorphan [DM]) starting at Visit 1 once daily for the first 3 days of treatment, then twice daily for up to 12 months. Subjects will return to clinic every week for 2 weeks, then every 2 weeks for the next 6 weeks, then monthly thereafter (Months 3-12). At all visits, subjects will be assessed for safety by adverse events (AE), vital signs, and the Columbia - Suicide Severity Rating Scale (C-SSRS). At Visit 1, and at Months 3, 6, 9, and 12, clinical laboratory examinations, electrocardiograms (EGCs), and physical examinations will also be performed. Patient- and clinician-reported assessments including the Montgomery-Åsberg Depression Rating Scale (MADRS), Sheehan Disability Scale (SDS), Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), and the Clinical Global Impression of Severity (CGI-S), will be assessed at Visit 1, Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, and 12. The Clinical Global Impression of Improvement (CGI-I) will be assessed at Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, and 12. At Week 6, subjects who did not previously participate in an AXS-05 study will be assessed for clinical improvement, defined as a 25% or more improvement in MADRS score. Subjects who do not show improvement will be discontinued from study and complete the remaining early termination assessments during Week 6. [redacted]
Planned Number of Subjects	This study will enroll approximately 1100 subjects, with 300 subjects treated for at least 6 months and 100 for 12 months. The study will be considered completed once 300 subjects are treated for at least 6 months and 100 for 12 months.
Study Centers	Approximately 50 U.S. study centers.
Diagnosis and Subject Selection Criteria **-Inclusion Criteria** **-Exclusion Criteria**	**Inclusion Criteria**: A subject will be eligible for participation if all of the following criteria are met: 1. Completed study AXS-05-301 or AXS-05-MDD-301 OR currently meets the DSM-5 criteria for MDD without psychotic features and has a MADRS score of at least 25 at Visit 1. 2. 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. 3. Removed in Amendment 1 4. Male or female outpatients, 18 to 65 years of age, inclusive.

	5. If female and of childbearing potential, has a negative urine pregnancy test result at Visit 1, 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:** A subject will be excluded from the study if the subject meets any of the following criteria: 1. 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). 2. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the investigator's brochure for AXS-05 tablets), to be an unsuitable candidate to receive AXS-05. 3. If the subject is currently receiving or plans to use drugs with known bupropion interactions (as listed in the Wellbutrin SR package insert), PI is aware of any potential drug interaction and has deemed the subject acceptable to participate. 4. 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. 5. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g. codeine, etc.), or any other ingredient in the study medication. 6. History of intolerance to bupropion or dextromethorphan. 7. 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. 8. Previously received treatment with any investigational drug (other than AXS-05) or device within 30 days of Visit 1.
Test Product, Dosage, and Mode of Administration	AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet, oral

Treatment Regimen	Doses will be titrated as follows: • Days 1 – 3: AXS-05 (105 mg bupropion, 45 mg DM) tablet, once daily, in the morning • Days 4 – end of study (maximum of 12 months): AXS-05 tablet, twice daily All doses should be taken orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. Twice daily doses should 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	The duration of participation will be up to 12 months.
Criteria for Evaluation	**Primary Safety Measures:** • Incidence of treatment-emergent AEs (TEAEs) following dosing with AXS-05. **Additional Safety Measures:** • Change in vital signs (blood pressure and heart rate) over time • Change in ECG findings over time • Change in clinical laboratory measures over time • Incidence of suicidal behavior, as identified via the C-SSRS **Efficacy Measures:** • Change in MADRS over time • Change in SDS over time • Change in Q-LES-Q-SF over time • CGI-S • CGI-I
Statistical Methods	**Analysis Populations:** The following analysis populations are planned for this study: ▪ *Safety Population*—the Safety Population will include all subjects who receive at least 1 dose of the study medication. ▪ *Intent-to-Treat (ITT) Population*—the ITT Population will include all subjects who receive at least 1 dose of the study medication and report at least one efficacy measurement. Descriptive statistics will be used for all variables and all data over time.
Sample Size Determination	This study will enroll approximately 1100 subjects, with 300 subjects treated for at least 6 months and 100 for 12 months. The study will be considered completed once 300 subjects are treated for at least 6 months and 100 for 12 months. This sample size will provide an adequate number of subjects exposed to assess the long-term safety of AXS-05.