

Document Type: Protocol and Statistical Analysis Plan

Protocol Title: An Open-Label Study to Assess the Long-term Safety of AXS-05 in Subjects with Dementia of the Alzheimer's Type

ClinicalTrials.gov Identifier: NCT06736509

Document Date: October 18, 2024

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-AD-305

[REDACTED]

[REDACTED]

DEVELOPMENT PHASE: Phase 3

PROTOCOL TITLE: An Open-Label Study to Assess the Long-term Safety of AXS-05 in Subjects with Dementia of the Alzheimer's Type

PROTOCOL VERSION: Original (V1.0)

PROTOCOL DATE: October 18, 2024



[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.

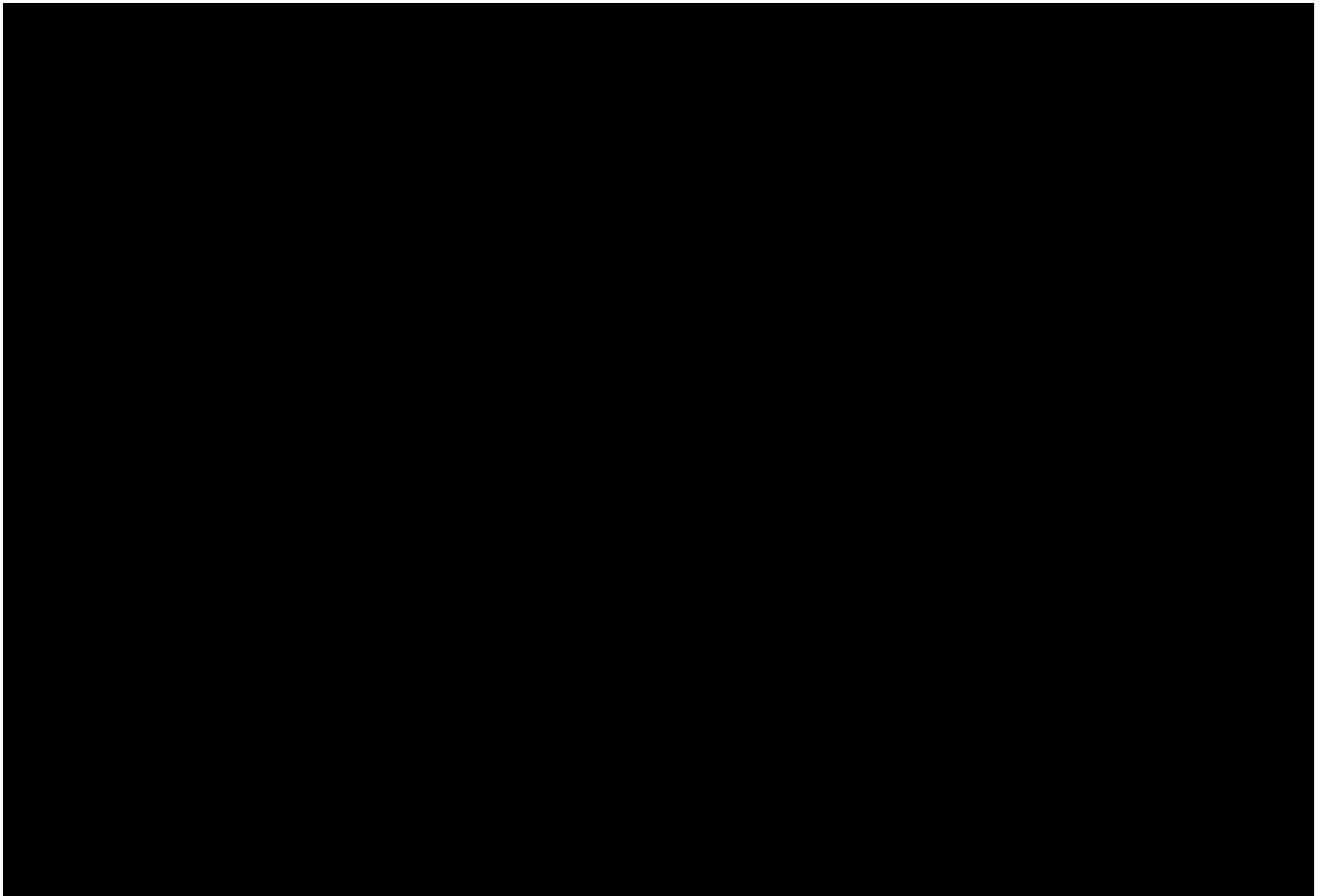
APPROVAL SIGNATURES

PROTOCOL NUMBER: AXS-05-AD-305

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Subjects with Dementia of the Alzheimer's Type

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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]

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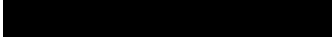
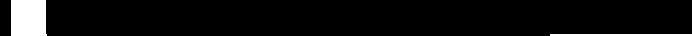
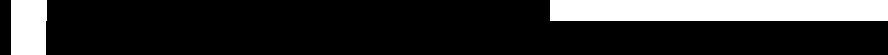
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INVESTIGATORS:

Multi-Center. A current list of clinical Investigators will be maintained in the Trial Master File (TMF).

1. SYNOPSIS

CLINICAL STUDY SYNOPSIS: AXS-05-AD-305	
Product Name/ Number	AXS-05 (dextromethorphan hydrobromide monohydrate and bupropion hydrochloride)
Protocol Number	AXS-05-AD-305
Protocol Title	An Open-Label Study to Assess the Long-term Safety of AXS-05 in Subjects with Dementia of the Alzheimer’s Type
Indication	Treatment of agitation associated with dementia of the Alzheimer’s type
Development Phase	3
Objective	The primary objective of this study is to evaluate the long-term safety of AXS-05 for the treatment of agitation associated with dementia of the Alzheimer’s type.
Study Design	<p>This is a multi-center, open-label trial to evaluate the long-term safety of AXS-05 in subjects with agitation associated with Alzheimer’s disease (AD). Eligible subjects will enter this study following completion of study AXS-05-AD-304 or exit from study AXS-05-AD-303 due to study closure. Subjects may enroll into this study at the final study visit of AXS-05-AD-304 or exit from AXS-05-AD-303. In order to maintain the blind from study AXS-05-AD-304 and AXS-05-AD-303, the dose of AXS-05 will be titrated* as follows:</p> <ul style="list-style-type: none"> • Day 2 – Day 7: AXS-05 (30 mg dextromethorphan HBr-105 mg bupropion HCl) once daily • Day 8 – Day 14: AXS-05 (30 mg dextromethorphan HBr-105 mg bupropion HCl) twice daily • Day 15 – Day 169: AXS-05 (45 mg dextromethorphan HBr-105 mg bupropion HCl) twice daily <p style="text-align: center;">[REDACTED]</p> <p>Subjects will have a visit (remote or in clinic – refer to Schedule of Assessments) every week for the first 4 weeks, then every 2 weeks for the next 4 weeks, then every 4 weeks through Week 24. At all visits, subjects will be assessed for safety by review of adverse events (AE) and assessment of the Columbia - Suicide Severity Rating Scale (C-SSRS). Additional safety assessments will include physical exams, vital signs, laboratory assessments, and electrocardiograms (ECGs) at in-clinic visits at Week 0, 12, and 24.</p> <p style="text-align: center;">[REDACTED]</p> <p>Caregivers will be provided with a Caregiver Diary and will be instructed to record daily: 1) any agitated or abnormal behaviors, if they occur, including the number of times they occurred that day, 2) the number of tablets of study drug taken and the time of administration, 3) use of any rescue medications, and 4) any changes in the subject’s physical status or mental status such as: dizziness, unusual weakness, falls, confusion, obvious worsening of memory problems, worsening agitation, any loss of consciousness, or seizures. Diaries may be used by the caregivers as recollection tools during the efficacy evaluations.</p>
Planned Number of Subjects	Subjects who complete study AXS-05-AD-304 or exit from AXS-05-AD-303 due to study closure, will be eligible to participate. No formal sample size calculation has been determined.
Study Centers	Up to 60 study centers in North America.

<p>Diagnosis and Subject Selection Criteria -Inclusion Criteria -Exclusion Criteria</p>	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> Completed the treatment period in study AXS-05-AD-304 or exited from study AXS-05-AD-303 due to study closure (subjects who completed 52 weeks of treatment in Study AXS-05-AD-303 or who discontinued due to protocol deviations or adverse events in Study AXS-05-AD-303 will not be eligible). A Caregiver willing to <ol style="list-style-type: none"> Communicate with site personnel and to comply with all required study procedures. Oversee administration and compliance with the subject’s study treatment. Agree to accompany the subject to all site visits, be available by telephone at designated times, and be able and willing to observe for possible adverse events and to report on the subject’s status. Fully understand the length of the trial. Subjects capable of signing consent (according to the opinion of the Investigator), or their authorized representatives, and their caregiver must both sign and receive a copy of the ICF after the nature and risks of study participation have been fully explained to them. <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> Caregiver is unwilling or unable, in the opinion of the Investigator, to comply with study instructions.  Any concurrent medical condition that might interfere with the conduct of the study, confound the interpretation of study results, or endanger the subject’s well-being. Initiation of a new medication since enrolling in AXS-05-AD-304 and/or AXS-05-AD-303 which may pose a safety risk when taken concurrently with AXS-05.
<p>Test Product, Dosage, and Mode of Administration</p>	<p>AXS-05 (30 mg dextromethorphan HBr-105 mg bupropion HCl) tablet, oral AXS-05 (45 mg dextromethorphan HBr-105 mg bupropion HCl) tablet, oral</p>
<p>Treatment Regimen</p>	<p>The treatment regimen is as follows:</p> <ul style="list-style-type: none"> Day 2 – Day 7: AXS-05 (30 mg dextromethorphan HBr-105 mg bupropion HCl) once daily Day 8 – Day 14: AXS-05 (30 mg dextromethorphan HBr-105 mg bupropion HCl) twice daily Day 15 – Day 169: AXS-05 (45 mg dextromethorphan HBr-105 mg bupropion HCl) twice daily  <p>All doses will be taken at least 8 hours apart.</p>
<p>Study Duration</p>	<p>This study will last up to 25 weeks in duration.</p>
<p>Criteria for Evaluation</p>	<p>Primary Outcome Measure: Safety, as assessed by adverse events.   </p>
<p>Statistical Methods</p>	<p>Analysis Populations: The following analysis populations are planned for this study:</p>

	<ul style="list-style-type: none">• <i>Safety Population</i>—the Safety Population will be the primary safety analysis population and will include all subjects who receive at least 1 dose of AXS-05.• <i>Intent-To-Treat Population (ITT)</i>—the ITT population will be the primary efficacy analysis population.• Additional populations may be included as appropriate. If required, these will be defined in the SAP <p>Safety Analysis:</p> <p>Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) reporting system. TEAEs are those that occur following the start of treatment with study drug through follow up (7 days after the last dose) and SAEs that occur from the start of treatment with study drug through 30 days after the last dose. The number and percentage of subjects with TEAEs will be displayed for each treatment group by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable.</p> <p>Descriptive summaries will be calculated, and data listings provided for hematologic, biochemical, and urinalysis laboratory parameters, C-SSRS, and vital signs measurements, as appropriate.</p>
Sample Size Determination	Subjects who complete the treatment period of study AXS-05-AD-304 or exit study AXS-05-AD-303 due to study closure, will be eligible to participate. No formal sample size calculation has been determined.