**Document Type:** Protocol and Statistical Analysis Plan

**Protocol Title:** ADVANCE-2: Addressing Dementia Via Agitation-Centered Evaluation: A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-05 for the Treatment of Alzheimer's Disease Agitation

**ClinicalTrials.gov Identifier:** NCT05557409

**Document Date:** June 2, 2022

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

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| COMPOUND NAME/NUMBER: | AXS-05 |
| PROTOCOL NUMBER: | AXS-05-AD-304 |
| [redacted] | [redacted] |
| DEVELOPMENT PHASE: | Phase 3 |
| PROTOCOL TITLE: | ADVANCE-2: Addressing Dementia Via Agitation-Centered Evaluation: A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-05 for the Treatment of Alzheimer's Disease Agitation |
| PROTOCOL VERSION: | Original (V1.0) |
| PROTOCOL DATE: | 02Jun2022 |

[redacted]

## APPROVAL SIGNATURES

PROTOCOL NUMBER: AXS-05-AD-304

PROTOCOL TITLE: ADVANCE-2: Addressing Dementia Via Agitation-Centered Evaluation: A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-05 for the Treatment of Alzheimer's Disease Agitation

PROTOCOL VERSION: Original (V1.0)

PROTOCOL DATE: 02Jun2022

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

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| SPONSORED BY: | Axsome Therapeutics, Inc. |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| INVESTIGATOR: | Multi-center. A list of sites will be housed in the Trial Master File. |

# 1. SYNOPSIS

| CLINICAL STUDY SYNOPSIS: AXS-05-AD-304 | |
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| **Product Name/ Number** | AXS-05 (dextromethorphan hydrobromide monohydrate - bupropion hydrochloride) |
| **Protocol Number** | AXS-05-AD-304 |
| **Protocol Title** | A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-05 for the Treatment of Alzheimer's Disease Agitation |
| **Indication** | Treatment of agitation associated with dementia of the Alzheimer's type |
| **Development Phase** | 3 |
| **Primary Objective** | The primary objective of the study is to evaluate the efficacy of AXS-05 compared to placebo on the change from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) total score in subjects with agitation associated with Alzheimer's disease. |
| **Study Design** | This trial is a multi-center, randomized, double-blind, placebo-controlled 5-week study evaluating the efficacy and safety of AXS-05 compared to placebo for the treatment of agitation associated with Alzheimer's disease (AD). Eligible subjects for this study must have a diagnosis of probable Alzheimer's disease (AD) and must have clinically meaningful agitation secondary to AD. Following screening procedures for assessment of inclusion and exclusion criteria, eligible subjects will be randomized in a 1:1 ratio to be treated with AXS-05 or placebo.<br>The primary efficacy endpoint is the change from baseline to Week 5 in the CMAI total score. [redacted]<br>**Screening Period**<br>Prior to baseline, all potential subjects will enter an up to 4-week screening period (Screening) to determine eligibility. In order to be eligible, subjects must have a diagnosis of probable AD according to the 2011 National Institute on Aging-Alzheimer Association (NIA-AA) criteria, and a diagnosis of agitation according to the International Psychogeriatric Association (IPA) provisional definition of agitation.<br>Eligible subjects must have symptoms of agitation (intermittently or constantly) at the time of screening and for at least 2 weeks prior to baseline, and the agitation symptoms must be severe enough such that they interfere with daily routine and for which a prescription medication is deemed indicated, in the opinion of the current treating physician. [redacted]<br>**Treatment Period**<br><u>Randomization</u><br>Eligible subjects who successfully complete Screening will be randomly assigned at the Baseline visit (Visit 2) to receive AXS-05 or placebo, orally, titrated to twice daily, in a 1:1 ratio, for a total of 5 weeks.<br>The randomization schedule will be computer-generated using a permuted block algorithm that will randomly allocate the study drug to randomization numbers. The randomization will be stratified by antipsychotic use (yes or no). |

Treatments

Doses will be titrated as follows:

- Days 1-7
  - AXS-05 group: 30 mg dextromethorphan HBr - 105 mg bupropion HCl once in the morning
  - Placebo group: placebo once in the morning
- Days 8-14
  - AXS-05 group: 30 mg dextromethorphan HBr - 105 mg bupropion HCl BID
  - Placebo group: placebo BID
- Days 15-36
  - AXS-05 group: 45 mg dextromethorphan HBr - 105 mg bupropion HCl BID
  - Placebo group: placebo BID

All doses will be taken at least 8 hours apart, orally.

All study drugs, including placebo, are of identical appearance in order to maintain the integrity of the blind.

Rescue Medication

Subjects will be allowed to receive oral lorazepam as rescue medication for the short-term treatment of symptoms of agitation if deemed necessary by the Investigator; but should be avoided on the day a study visit occurs until after assessments are complete. Lorazepam (0.5 mg tablets) will be administered in a total dose up to 1.5 mg/day and not to exceed 3 days in a 7-day period. Caregivers must record concomitant use of rescue medication (i.e., lorazepam) in the Caregiver Diary.

**Assessments and Visits**

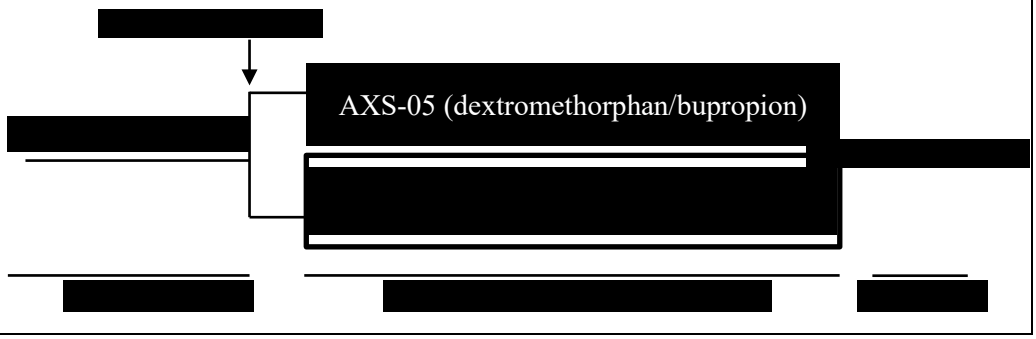
Study visits will occur at Screening (Visit 1), Baseline (Day 1, Visit 2), and on Days 8, 15, 22, and 36 (Visits 3-6). Study procedures will be performed, and questionnaires for the evaluation of efficacy parameters will be administered, during study visits. At the Week 5 visit, the subject will have the option to enter the open-label extension study, AXS-05-AD-303. If they do not enter the open-label extension study, they will have a remote safety follow-up visit (Visit 7, Day 43) 1 week after the last dose of study drug.

Caregivers will be provided with a Caregiver Diary at each study visit 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) the dose and time of rescue medication (i.e., lorazepam) administered if applicable, and 4) any changes in the subject's physical status or mental status such as dizziness, unusual weakness, falls, confusion or obvious worsening of memory problems, worsening agitation, any loss of consciousness, or seizures. Diaries will be reviewed during study visits.

A blood sample for cytochrome P450 2D6 (CYP2D6) genotyping will be collected at the Baseline visit. Blood samples for measurement of study drug concentrations will be collected on Day 15 (Visit 4) and on Day 36 (Visit 6).

The study design is summarized in the Figure below.

**AXS-05-AD-304 Study Design**



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| **Planned Number of Subjects** | Up to 350 subjects will be randomized (175 per arm). |
| **Study Centers** | Approximately 60 study centers in the U.S. and Canada. |
| **Diagnosis and Subject Selection Criteria**<br>**-Inclusion Criteria**<br>**-Exclusion Criteria** | **Inclusion Criteria**:<br>1. Male or female outpatients, 65 to 90 years of age, inclusive.<br>2. Diagnosis of probable Alzheimer's disease (AD) based on the 2011 National Institute on Aging-Alzheimer Association (NIA-AA) criteria.<br>3. Clinically significant agitation, at the time of screening and for at least 2 weeks prior to baseline, that interferes with daily routine activities and for which a prescription medication is deemed indicated, in the opinion of the investigator.<br>4. The diagnosis of agitation must meet the International Psychogeriatric Association (IPA) provisional definition of agitation, as evidenced by each of the following:<br>A. The subject exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g., rapid changes in mood, irritability, outbursts), and the behavior has been persistent or frequently recurrent for at least 2 weeks and represents a change from the subject's usual behavior:<br>a) Physical aggression (e.g., grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property)<br>b) Verbal aggression (e.g., yelling, speaking in an excessively loud voice, using profanity, screaming, shouting)<br>c) Excessive motor activity (e.g., pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms)<br>B. Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to cognitive impairment and including at least one of the following:<br>a) Significant impairment in interpersonal relationships.<br>b) Significant impairment in other aspects of social functioning.<br>c) Significant impairment in ability to perform or participate in daily living activities.<br>C. The agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance.<br>[redacted]<br>[redacted]<br>7. Caregiver must be:<br>a) A family member who has been providing care to the subject for at least 3 months prior to Screening.<br>b) Knowledgeable of the subject and reliable in providing care to the subject.<br>[redacted]<br>d) Capable, in the opinion of the Investigator, of providing an adequate rating of the subject's condition.<br>8. Caregiver must also:<br>a) Be able and willing to communicate with site personnel, to comply with all required study procedures including not administering any prohibited medications during the course of the study, and to oversee the subject's compliance with the study treatment. |

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| | b) Agree to accompany the subject to all 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.<br>c) Fully understand the length of the trial.<br>d) Agree to undergo training in recognizing agitation symptoms and in rating of the scales used in the study.<br>e) Agree to comply with all study instructions.<br>9. Caregiver signed and received a copy of a caregiver's ICF after the nature and risks of study participation had been fully explained.<br>10. 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 subject's ICF after the nature and risks of study participation have been fully explained to them.<br>11. Patients who are capable of providing assent but not capable of signing the ICF, according to the investigator, should provide assent for study participation.<br>a. Patients who sign the ICF are not required to provide a separate assent.<br>b. Patients who are not capable of providing assent are still allowed to participate provided the patient's authorized representative agrees to participation. Investigators must document the reasons for any patient who is unable to provide assent and maintain this documentation with the consent/assent documents.<br>12. The patient has stable cardiac, pulmonary, hepatic, and renal function.<br>13. Subjects currently receiving a drug for the treatment of Alzheimer's disease (e.g., donepezil, rivastigmine, galantamine, memantine) are eligible provided they have been on a stable dose of these medications for at least 8 weeks prior to baseline.<br>14. Patients currently taking allowed medications for the treatment of agitation secondary to Alzheimer's disease (e.g., antipsychotics, buspirone) are eligible provided they have been on a stable dose for at least 4 weeks prior to baseline. Antipsychotics which are primarily metabolized by CYP2D6 are exclusionary (see permitted and prohibited medications section). Subjects who have recently discontinued these medications must be off them for at least 4 weeks prior to baseline.<br>15. Concomitant use of low dose trazodone (up to 50 mg/day), melatonin, eszopiclone, zolpidem, zopiclone or zaleplon for nighttime management of insomnia, provided the dose and regimen have been stable for at least 4 weeks prior to baseline and remain stable throughout the study, is allowed. Contact the medical monitor, or other appropriate designee, regarding the use of other sleep aids.<br>[redacted]<br>**Exclusion Criteria:**<br>1. Caregiver is unwilling or unable, in the opinion of the Investigator, to comply with study instructions.<br>2. Subject has dementia predominantly of non-Alzheimer's type (e.g., vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia).<br>3. Subject is hospitalized in a mental health facility (e.g., psychiatric hospital or ward), or living alone.<br>4. Subject has symptoms of agitation that are not secondary to Alzheimer's disease (e.g., pain, other psychiatric disorder or delirium due to a metabolic disorder, systemic infection or substance-induced). |

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| | 5. History or current clinical symptoms of schizophrenia, schizoaffective disorder, or bipolar disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).<br>6. History of alcohol or substance use disorder (other than nicotine or caffeine) within 1 year of baseline.<br>7. Use of serotonergic medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are prohibited to avoid the risk of serotonin syndrome. These products are exclusionary if used within 2 weeks, or 5 half-lives, whichever is longer, of baseline.<br>8. Current use, or use within 14 days before study drug dosing, of monoamine oxidase inhibitors (MAOIs), linezolid, or intravenous methylene blue.<br>9. History of seizure disorder, anorexia nervosa or bulimia; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates and 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).<br>10. Any concurrent medical condition that might interfere with the conduct of the study, confounds the interpretation of study results, or endangers the subject's well-being. This includes a history of malignancy within the last two years (except skin basal-cell carcinoma or local prostate cancer), or any significant hematologic, endocrine/metabolic (e.g., poorly controlled diabetes), cardiovascular (e.g., poorly controlled hypertension, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease), unstable or progressive pulmonary, renal, hepatic, gastrointestinal or neurologic, or other chronic disease. Certain other non-metastatic cancer may be allowed (each case is to be evaluated individually with the medical monitor).<br>11. Hypertension defined as resting, sitting systolic blood pressure (BP) ≥150 mm Hg or diastolic BP ≥ 95 mm Hg. Subjects with systolic BP >134 mm Hg or diastolic BP > 85 mm Hg should be receiving adequate treatment for hypertension. Blood pressure values may be confirmed by serial assessments (at least 30 minutes apart), if needed.<br>12. 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).<br>13. Narrow-angle glaucoma without a patent iridectomy.<br>14. Known human immunodeficiency virus (HIV) infection.<br>15. Known history of hepatitis B or C infection.<br>16. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase and/or alanine aminotransferase) results > 2.0 x ULN.<br>17. Any clinically significant abnormality on the screening laboratory tests, as assessed by the study Investigator and/or the medical monitor.<br>18. History of allergy or hypersensitivity to bupropion, dextromethorphan, any other ingredient of the study drug, [redacted]<br>19. History of intolerance to bupropion or dextromethorphan.<br>20. Subjects who have received dextromethorphan co-administered with quinidine (e.g., Nuedexta®) and did not respond to treatment.<br>21. Subjects who have been taking disallowed concomitant medications within 2 weeks or 5 half-lives, whichever is longer, prior to baseline (see permitted and prohibited medications |

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| | section).<br>22. Subjects currently being treated, or who have been treated with any investigational product (drug or device) within 30 days or 5 half-lives, whichever is longer, of Baseline.<br>23. Prior participation in an AXS-05 clinical trial.<br>24. Subjects determined to have a high imminent risk of falls during the study based on a clinical evaluation by the Investigator.<br>25. Subjects with history of postural syncope, or any history of unexplained syncope (evaluated on a case-by-case basis) within 12 months of Baseline.<br>26. Subjects must not show current and clinically significant symptoms of major depressive disorder, or risk of suicide or harm to self or others. |
| **Test Product, Dosage, and Mode of Administration** | AXS-05 (titration dose: 30 mg dextromethorphan HBr-105 mg bupropion HCl) tablet, oral<br>AXS-05 (target dose: 45 mg dextromethorphan HBr-105 mg bupropion HCl) tablet, oral |
| **Reference Therapies, Dosage, and Mode of Administration** | Placebo matching tablet, oral |
| **Treatment Regimen** | <u>Days 1-7 (Week 1)</u><br>• AXS-05 group: 30 mg dextromethorphan HBr - 105 mg bupropion HCl once in the morning<br>• Placebo group: placebo once in the morning<br><u>Days 8-14 (Week 2)</u><br>• AXS-05 group: 30 mg dextromethorphan HBr - 105 mg bupropion HCl BID<br>• Placebo group: placebo BID<br><u>Days 15-36 (Week 3-5)</u><br>• AXS-05 group: 45 mg dextromethorphan HBr - 105 mg bupropion HCl BID<br>• Placebo group: placebo BID<br>All doses will be taken at least 8 hours apart, orally. |
| **Study Duration** | This study will last up to 10 weeks including an up to 4-week Screening period, a 5-week double-blind treatment period, followed by a 1-week follow-up visit. |
| **Criteria for Evaluation** | **Primary Outcome Measure:**<br>Cohen-Mansfield Agitation Inventory (CMAI)<br>**Primary Endpoint**:<br>▪ CMAI total score, change from Baseline to Week 5<br>[redacted] |

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| **Safety Measures** | ▪ Incidence of Treatment Emergent Adverse Events (TEAEs)<br>▪ Clinical laboratory test results<br>▪ Vital sign measurements<br>▪ ECG findings<br>▪ Columbia – Suicide Severity Rating Scale (C-SSRS) |
| **Statistical Methods** | **Analysis Populations:**<br>The following analysis populations are planned for this study:<br>▪ *Modified Intent-to-Treat (mITT) Population*—the mITT will be the primary efficacy analysis population and will consist of all subjects who are randomized, subsequently take at least 1 dose of the study drug, and have at least 1 post-Baseline efficacy assessment.<br>▪ *Intent-to-Treat Population*—the ITT will include all subjects who are randomized.<br>▪ *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.<br>**Primary Efficacy Analysis:**<br>The primary endpoint will be the change from Baseline (Day 1) to Week 5 in the CMAI total score. The primary comparison will be AXS-05 versus placebo.<br>The changes from Baseline in the CMAI total score will be analyzed using a Mixed Model with Repeated Measures (MMRM). This model will include treatment, week, and treatment-by-week interaction as factors, Baseline value as a covariate, and subject as a random effect. Treatment effects and the differences between treatments will be estimated using the least-square mean estimates and will be reported together with the 2-sided 95% confidence interval of the treatment difference. The null hypothesis of no treatment difference will be tested at a two-sided significance level of 0.05.<br>**Safety Analysis:**<br>Descriptive summaries will be calculated for each safety parameter. |
| **Sample Size Determination** | Up to approximately 300 subjects will be randomized (150 per arm) and will provide 90% power to detect a treatment difference for the primary efficacy variable (change from baseline in CMAI total score at Week 5) at a two-sided significance level of 0.05. [redacted] |