Document Type: Protocol and Statistical Analysis Plan

Protocol Title: ADVANCE: 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 Agitation in Subjects with Dementia of the Alzheimer's Type

ClinicalTrials.gov Identifier: NCT03226522

Document Date: March 16, 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-AD-301
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 2/3
PROTOCOL TITLE:	ADVANCE: 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 Agitation in Subjects with Dementia of the Alzheimer's Type
PROTOCOL VERSION:	Amendment 3
PROTOCOL DATE:	March 16, 2020

AXSOME
THERAPEUTICS

[redacted]

APPROVAL SIGNATURES

PROTOCOL NUMBER: AXS-05-AD-301

PROTOCOL TITLE: A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-05 for the Treatment of Agitation in Subjects with Dementia of the Alzheimer's Type

PROTOCOL VERSION: Amendment 3

PROTOCOL DATE: March 16, 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]
INVESTIGATORS:	Multi-Center

1. SYNOPSIS

CLINICAL STUDY SYNOPSIS: AXS-05-AD-301	
Product Name/ Number	AXS-05 (bupropion hydrochloride and dextromethorphan hydrobromide monohydrate)
Protocol Number	AXS-05-AD-301
Protocol Title	A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of AXS-05 for the Treatment of Agitation in Subjects with Dementia of the Alzheimer's Type
Indication	Treatment of agitation associated with dementia of the Alzheimer's type
Development Phase	2/3
Objective	The primary objective of the study is to evaluate the efficacy and safety of AXS-05 compared to placebo and bupropion sustained release (SR) for the treatment of agitation in subjects with dementia of the Alzheimer's type.
Study Design	This trial is a multi-center, randomized, double-blind, double-dummy, placebo-controlled study, consisting of 5 weeks of treatment. 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 1:1:1 ratio to be treated with AXS-05, bupropion sustained release (SR), or placebo. As part of protocol amendment 2, randomization to the bupropion arm was discontinued. The primary efficacy endpoint is the change from baseline to Week 5 in the Cohen-Mansfield Agitation Inventory (CMAI) total score. [redacted] **Screening Period** Prior to randomization, 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. Eligible subjects must have symptoms of agitation (intermittently or constantly) at the time of screening and for at least 2 weeks prior to randomization, 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] **Treatment Period** <u>Randomization</u> Eligible subjects who successfully complete Screening will be randomly assigned at the baseline visit (Baseline) to receive AXS-05, bupropion SR, or placebo, orally, twice daily, in a 1:1:1 ratio, for 5 consecutive weeks. As part of protocol amendment 2, randomization to the bupropion arm was discontinued. 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 region (US or Ex-US) and by antipsychotic use (yes or no).

Treatments

Doses will be titrated as follows:

[redacted]

- AXS-05 group: 105 mg bupropion/45 mg dextromethorphan BID
- Bupropion group: 105 mg bupropion BID
- Placebo group: placebo BID

All doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or post-prandial) with water.

All study medication including AXS-05 tablets, bupropion SR tablets, and placebo tablets are of identical appearance in order to maintain the integrity of the blind.

Rescue Medication

Patients 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. 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 lorazepam in the Caregiver Diary.

Assessments and Visits

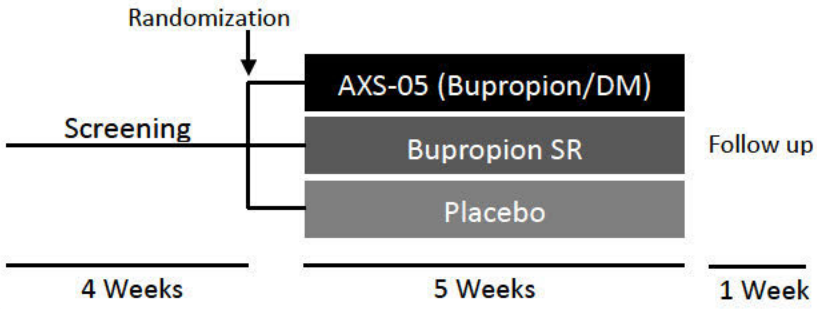
Study visits will occur at Screening (Visit 1), Baseline (Day 1, Visit 2), and on Days 8, 15, 22, 36 (Visits 3-6). Study procedures will be performed, and questionnaires for the evaluation of efficacy parameters will be administered during study visits. A safety follow-up phone call (Visit 7) will be conducted 1 week after the last dose of study drug (Day 43).

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 medication taken and the time of administration, 3) the dose of rescue medication administered and the time of administration if administered, 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-301 Study Design



Planned Number of Subjects	Approximately 435 subjects (145 per arm) will be randomized to achieve approximately 300 completed subjects. As part of protocol amendment 2, randomization to the bupropion arm was discontinued.
Study Centers	Up to approximately 60 study centers in the U.S., Canada, and Australia.
Diagnosis and Subject Selection Criteria **-Inclusion Criteria** **-Exclusion Criteria**	**Inclusion Criteria**: 1. Male or female outpatients, 65 to 90 years of age, inclusive. 2. Diagnosis of probable Alzheimer's disease (AD) based on the 2011 National Institute on Aging-Alzheimer Association (NIA-AA) criteria. 3. Clinically significant agitation, at the time of screening and for at least 2 weeks prior to randomization, that interferes with daily routine activities and for which a prescription medication is deemed indicated, in the opinion of the investigator. 4. The diagnosis of agitation must meet the International Psychogeriatric Association (IPA) provisional definition of agitation, as evidenced by each of the following: A. The patient 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 patient's usual behavior: 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) b) Verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting) c) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms) 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: a) Significant impairment in interpersonal relationships. b) Significant impairment in other aspects of social functioning. c) Significant impairment in ability to perform or participate in daily living activities. C. The agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance. [redacted] 7. Caregiver must be: a) A family member who has been providing care to the patient for at least 3 months prior to Screening. b) Knowledgeable of the patient, and reliable in providing care to the patient. c) In regular contact with the patient and spend a minimum of 16 hours per week (a minimum of 4 hours on 4 separate days) with the patient. d) Capable, in the opinion of the investigator, of providing an adequate rating of the patient's condition. 8. Caregiver must also: a) Be able and willing to communicate with site personnel and to comply with all required study procedures including not administering any prohibited medications during the course of the study, and to oversee the patient's compliance with the study treatment.

b) Agree to accompany the patient 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 patient's status.
c) Fully understand the length of the trial.
d) Agree to undergo training in recognizing agitation symptoms and in rating of the scales used in the study.

9. Caregiver signed and received a copy of a caregiver's ICF after the nature and risks of study participation had been fully explained.
10. Patients capable of signing consent (according to the investigator), or their authorized representatives, signing and receiving a copy of the patient's ICF after the nature and risks of study participation have been fully explained to them.
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.
    a) Patients who sign the ICF are not required to provide a separate assent.
    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.
12. The patient has stable cardiac, pulmonary, hepatic, and renal function.
13. Patients currently receiving a drug for the treatment of AD (e.g., donepezil, rivastigmine, galantamine, memantine) are eligible provided they have been on a stable dose of these medications for at least 2 months prior to randomization.
14. Patients currently taking allowed medications for the treatment of agitation secondary to AD (e.g., antipsychotics, buspirone) are eligible provided they have been on a stable dose for at least 4 weeks prior to randomization. Patients who have recently discontinued these medications must be off them for at least 4 weeks prior to randomization. Antipsychotics which are primarily metabolized by CYP2D6 are exclusionary (see permitted and prohibited medications section).
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 1 month prior to randomization and remain stable throughout the study, is allowed. Contact the medical monitor regarding the use of other sleep aids.

[redacted]

Exclusion Criteria:

1. Caregiver is unwilling or unable, in the opinion of the investigator, to comply with study instructions.
2. Patient has dementia predominantly of non-Alzheimer's type (e.g., vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia).
3. Patient is hospitalized in a mental health facility (e.g., psychiatric hospital or ward), or living alone.
4. Patient has symptoms of agitation that are not secondary to AD (e.g., pain, other psychiatric disorder or delirium due to a metabolic disorder, systemic infection or substance-induced).
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).
6. History of alcohol or substance use disorder (other than nicotine or caffeine) within 1 year

	of randomization. 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 randomization. 8. Current use, or use within 14 days before study drug dosing, of monoamine oxidase inhibitors (MAOIs), linezolid, or intravenous methylene blue. 9. History of seizure disorder, anorexia nervosa or bulimia; undergoing abrupt discontinuation of alcohol, benzodiazapines, 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). 10. Any concurrent medical condition that might interfere with the conduct of the study, confounds the interpretation of study results, or endangers the patient's well-being. This includes a history of malignancy within the last two years (except skin basal-cell carcinoma or untreated 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 to be evaluated individually with medical monitor. 11. Hypertension defined as resting, sitting systolic blood pressure (BP) ≥150 mm Hg or diastolic BP ≥ 95 mm Hg. Patients 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. 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). 13. Narrow-angle glaucoma without a patent iridectomy. 14. Known human immunodeficiency virus (HIV) infection. 15. Known history of hepatitis B or C infection. 16. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase and/or alanine aminotransferase) results > 2.0 x ULN. 17. Any clinically significant abnormality on the screening laboratory tests, as assessed by the study investigator and/or the medical monitor. 18. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g. codeine, etc.), or any other ingredient in the study medication. 19. History of allergy to benzodiazepines (e.g., lorazepam). 20. History of intolerance to bupropion or dextromethorphan. 21. Patients who have received dextromethorphan co-administered with quinidine (e.g. Nuedexta®) and did not respond to treatment. 22. Patients who have been taking disallowed concomitant medications within 2 weeks or 5 half-lives, whichever is longer, prior to Baseline. 23. Patients 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. 24. Patients determined to have a high imminent risk of falls during the study based on a clinical

	evaluation by the investigator. 25. Patients with history of postural syncope, or any history of unexplained syncope (evaluated on a case by case basis) within 12 months of Baseline. 26. Patient must not show current and significant symptoms of a major depressive disorder or clinically significant risk of suicide or harm to self or others.
Test Product, Dosage, and Mode of Administration	[redacted] Treatment A (target dose): AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet, oral
Reference Therapies, Dosage, and Mode of Administration	Treatment B: Bupropion SR (105 mg) matching tablet, oral Treatment C: Placebo matching tablet, oral
Treatment Regimen	[redacted] • AXS-05 group: 105 mg bupropion/45 mg dextromethorphan BID • Bupropion group: 105 mg bupropion BID • Placebo group: placebo BID All doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or post-prandial) with water.
Study Duration	Up to 10 weeks: up to 4 weeks Screening, followed by 5 weeks of treatment, followed by a 1-week follow-up visit.
Criteria for Evaluation	**Primary Outcome Measure:** Cohen-Mansfield Agitation Inventory (CMAI) **Primary Endpoint**: ▪ CMAI total score, change from Baseline to Week 5 **Key Secondary Endpoints:** ▪ Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC Agitation) [redacted] **Secondary Endpoints**: [redacted]

	[redacted]
Safety Measures	▪ Adverse Event (AE) recording ▪ Adverse Dropouts (ADOs) ▪ Incidence of Treatment Emergent Adverse Events (TEAEs) ▪ Clinical laboratory test results ▪ Vital sign measurements ▪ ECG findings ▪ Physical examination findings ▪ 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 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 ▪ *Intent-to-Treat Population*—the ITT will include all subjects who are randomized ▪ *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 **Primary Efficacy Analysis:** 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. 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. **Safety Analysis:** 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. Descriptive summaries will be calculated, and data listings provided for hematologic, biochemical, and urinalysis laboratory parameters, and vital signs measurements, as appropriate.
Sample Size Determination	Approximately 300 completed subjects (100 per treatment group) will provide 90% 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. In the sample size calculation, it was assumed the effect size was 0.46. Approximately 435 subjects (145 subjects each in the AXS-05, bupropion SR, and placebo arms) will be randomized to achieve approximately 300 completed subjects, assuming an approximately 30% drop-out rate. As part of protocol amendment 2, randomization to the bupropion arm was discontinued.

Schedule of Assessments

Visit	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 / ET[a]	Follow-up[b] Visit 7
Study Day	**-28 to -1**	**1**	**8 (±3)**	**15 (±3)**	**22 (±3)**	**36 (±3)**	**43 (±3)**
End of Week	**Weeks -4 to -1**		**Week 1**	**Week 2**	**Week 3**	**Week 5**	**Week 6**
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Medical history and demographics	X						
Physical examination[c]	X					X	
Vital signs[d]	X	X[e]	X	X	X	X	
Electrocardiogram	X					X	
Review previous and concomitant medications	X	X	X	X	X	X	X
Height and weight	X					X	
Clinical laboratory tests[f]	X					X	
[redacted]							
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	
[redacted]							
Randomization		X					
Cohen-Mansfield Agitation Inventory (CMAI)		X	X	X	X	X	
[redacted]							
Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC)		X				X	
Administer first dose of study medication in clinic		X[h]					
Administer last dose of study medication in clinic						X	
Review of adverse events		X[i]	X	X	X	X	X
Blood sample for drug concentration				X		X[j]	
Blood sample for CYP2D6 genotyping		X					
[redacted]							
Caregiver to Complete Daily Caregiver Diary[g]		X	X	X	X	X	
Review and return study medication and Caregiver Diary			X	X	X	X	
Dispense study medication		X	X	X			

a Early Termination (ET) visit for subjects who withdraw prior to study completion, the Follow-up Visit will occur 1 week after ET.
b Follow up visit may be conducted by phone. If the patient reports AEs that require follow-up an in-clinic visit should be performed.
c A complete physical examination (excluding breast and genitourinary examination) will be performed at Screening and a brief physical examination will be performed at Week 5 or at Early Termination.
d Vital signs, including seated and orthostatic blood pressure and pulse, respiratory rate, and oral temperature, will be measured.
e On Day 1, vital signs should be collected pre-dose and at least 1 hour following the dose.
f Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.
g A Caregiver Diary will be used to record the number of tablets of study medication and rescue medication (lorazepam) administered and the time of administration, adverse events, and subject behaviors. Study personnel will train caregivers how to complete the diary, retraining to occur as needed.
h Subjects should be monitored in the clinic after the first dose. At a minimum, vital signs should be recorded 1 hour following the dose. If any changes in the subjects health status, subjects should stay in clinic for at least 3 hours following the dose and have additional safety assessments performed, such as ECG evaluation and/ or serum electrolytes, as appropriate.
i During Week 1, sites are encouraged to contact subjects by phone to review and follow up on AEs.
j At visit 6, a pre- and post-dose (within 3 hours after dosing) sample should be collected.