Document Type: Protocol

Protocol Title: A Multi-center, Randomized, Double-blind, Placebo-controlled, 3-Week Crossover Study to Assess the Efficacy and Safety of AXS-12 in Subjects with Cataplexy and Excessive Daytime Sleepiness in Narcolepsy

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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-12
PROTOCOL NUMBER:	AXS-12-201
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	A Multi-center, Randomized, Double-blind, Placebo-controlled, 3-Week Crossover Study to Assess the Efficacy and Safety of AXS-12 in Subjects with Cataplexy and Excessive Daytime Sleepiness in Narcolepsy
PROTOCOL VERSION:	Amendment 2
PROTOCOL DATE:	25 Apr 2019

AXSOME
THERAPEUTICS

[redacted]

APPROVAL SIGNATURES

PROTOCOL NUMBER:	AXS-12-201
PROTOCOL TITLE:	A Multi-center, Randomized, Double-blind, Placebo-controlled, 3-Week Crossover Study to Assess the Efficacy and Safety of AXS-12 in Subjects with Cataplexy and Excessive Daytime Sleepiness in Narcolepsy
Protocol Version:	Amendment 2
Protocol Date:	25 Apr 2019

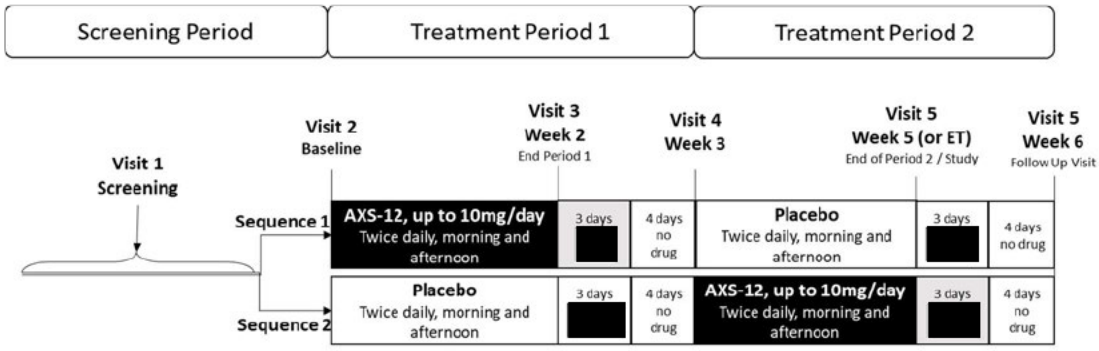
I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Study Contact and Details

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

1. SYNOPSIS

PRODUCT NAME/NUMBER	AXS-12 (reboxetine)
PROTOCOL NUMBER	AXS-12-201
PROTOCOL TITLE	A Multi-center, Randomized, Double-blind, Placebo-controlled, 3-Week Crossover Study to Assess the Efficacy and Safety of AXS-12 in Subjects with Cataplexy and Excessive Daytime Sleepiness in Narcolepsy
INDICATION	Treatment of Cataplexy in Narcolepsy
DEVELOPMENT PHASE	Phase 2
OBJECTIVES	**Primary Objective:** To assess the effect of AXS-12 as compared to placebo on the number of cataplexy attacks as recorded in a Sleep and Symptom Daily Diary. **Secondary Objectives:** To assess the effect of AXS-12 on: [redacted] - Patient Global Impression of Severity (PGI-S) - Hamilton Rating Scale for Depression (HAM-D) - Epworth Sleepiness Scale (ESS) - Narcolepsy Symptom Assessment Questionnaire (NSAQ) - Ability to Concentrate item of the NASQ
STUDY DESIGN	This study is a three-week, crossover, multi-center, randomized, double-blind, placebo-controlled proof-of-concept Phase 2 trial to assess the safety and efficacy of AXS-12 in narcoleptic subjects with cataplexy and excessive daytime sleepiness (EDS). Eligible subjects must have a diagnosis of narcolepsy per the International Classification of Sleep Disorders, Third Edition (ICSD-3) criteria, and exhibit symptoms of both cataplexy and EDS. Subjects meeting the entry criteria will be randomized in a 1:1 ratio either to placebo for three weeks followed by AXS-12 (up to 10 mg daily) for three weeks, or to AXS-12 (up to 10 mg daily) for three weeks followed by placebo for three weeks. Study medication will be down-titrated during the third week of each three-week treatment period. The primary endpoint will be the change in the number of cataplexy attacks as recorded in a Sleep and Symptom Daily Diary. Secondary outcome measures will include the Maintenance of Wakefulness Test (MWT), Patient Global Impression of Severity (PGI-S), Epworth Sleepiness Scale (ESS), Hamilton Rating Scale for Depression (HAM-D), Narcolepsy Symptom Assessment Questionnaire (NSAQ), and the Ability to Concentrate item of the NASQ. **Screening Period** All subjects will enter an up to three-week screening period (Screening, Visit 1) to determine eligibility. The screening period may last across multiple days / visits. During the screening period, an all-night polysomnography (PSG) followed by multiple sleep latency test (MSLT) may be required to confirm eligibility. Longer screening periods may be allowed to ensure washout of prior cataplexy medications. **Treatment Periods** Subjects meeting the entry criteria will be randomized in a 1:1 ratio either to placebo for three weeks followed by AXS-12 (up to 10 mg daily) for three weeks, or to AXS-12 (up to 10 mg daily) for three weeks followed by placebo for three weeks. Study medication will be down-titrated during the third week of each three-week treatment period. Doses will be titrated to a target dose of 10 mg [redacted] during

	each treatment period. [redacted] Subjects will be monitored for safety and tolerability at each titration step. [redacted] Reboxetine tablets will be over-encapsulated for blinding purposes. All study medication will be of similar appearance in order to maintain the integrity of the blind. [redacted] **Assessments and Visits** On Day 1 (Visit 2) eligible subjects will undergo baseline assessments and administration of the first dose of study drug in clinic. Subsequent study visits will occur on Days 15, 22, 36, and 42 (Visits 3-6). Study procedures and assessments will be performed during study visits as outlined in the Schedule of Assessments. **Study Design Schematic** 
PLANNED NUMBER OF SUBJECTS	Approximately 20 subjects will be enrolled in this study.
STUDY CENTERS	Up to 10 study sites in the United States and Australia.
STUDY ENTRY CRITERIA	Inclusion criteria: A subject will be eligible for entry into the study if all of the following inclusion criteria are met: 1. Is male or female between 18 and 70 years of age, inclusive. 2. A primary diagnosis of narcolepsy with cataplexy that meets International Classification of Sleep Disorders, Third Edition (ICSD-3) criteria determined, in part, by an overnight PSG and next-day MSLT with 2 or more sleep-onset rapid eye movement (REM) periods (SOREMPs) with mean sleep latency in the pathological range (i.e. < 8 minutes). Documentation of narcolepsy with cataplexy by PSG and MSLT within 10 years of Screening is acceptable for confirmation of diagnosis. 3. Current continuing presence of EDS as defined by subject report for the last 3 months and an Epworth Sleepiness Scale (ESS) > 10 at Screening and Baseline. 4. Documented minimum of 7 cataplexy attacks per week (or 14 across two weeks) as recorded in the subject's daily diary during the Screening period. 5. If female and of childbearing potential, is nonlactating and nonpregnant (has negative pregnancy test results at Screening and Baseline). 6. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing one or more of the following medically acceptable methods of birth control:

	• Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before study drug administration. • Total abstinence from sexual intercourse since the last menses before study drug administration, abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. • Intrauterine device. • Vasectomized partner. • Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream). 7. Is willing and able to attend study visits, including overnight sleep stays, comply with study drug dosing, complete the daily cataplexy diary and all other study-related assessments. 8. Is able to provide written informed consent to participate in the study and able to understand the procedures and study requirements. 9. Is willing to voluntarily sign and date an informed consent form that is approved by a human research ethics committee before the conduct of any study procedure. <u>Exclusion criteria</u>: A subject will not be eligible for study entry if any of the following exclusion criteria are met: 1. Current or prior use of reboxetine. 2. Concomitant sleep disorder. Subjects with untreated mild sleep apnea (< 15 events per hour) are allowed. Subjects receiving treatment for mild to moderate sleep apnea (< 30 events per hour) are allowed if the subject is receiving stable treatment. 3. Concurrent use of any of the following medications: sodium oxybate, stimulants, anticonvulsants, clonidine, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine re-uptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), hypnotics, anxiolytics, sedating antihistamines, antipsychotics, or any other experimental medications designed to treat narcolepsy, cataplexy or any other condition. A longer screening period will be allowed, as needed, to ensure subjects have withdrawn any of the above medications for at least 5 half-lives, or 5 days, whichever is longer. Note: Modafinil and armodafinil are allowed provided the dose is stable for at least 3 weeks before treatment start and maintained through the study duration. 4. History of seizure or other convulsive disorder. 5. Diagnosis of cancer (other than basal cell carcinoma) within the last 5 years. Subjects who have received definitive treatment, such as curative surgery more than 6 months ago, with no known recurrence may be included following consultation with the Sponsor. 6. Bilirubin, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase levels >2 times the upper limit of normal. 7. Clinically significant hypertension (as defined by the PI), uncontrolled hypertension, or a history of cardiovascular disease (e.g., myocardial infarction, angina, dysrhythmias, cardiac failure). 8. Current sign or symptom of severe and/or progressive or uncontrolled: hepatic, renal, gastrointestinal, endocrine, hematological, pulmonary, or neurological disease. 9. Clinically significant psychiatric disorder (eg, schizophrenia, bipolar disorder, or panic disorder) including a lifetime history of manic or psychotic episodes or who are at significant risk of self-injury, suicide, or aggression towards others. Significant risk of suicide is determined by the subject responding "yes" to question 4 or question 5 on the screening C-SSRS at Visit 1 or Visit 2, and the most recent episode occurred in the last 12 months. 10. History of narrow angle glaucoma. 11. Any other clinically significant medical condition or clinical laboratory abnormality that would in the investigator's judgment interfere with the subject's ability to participate in the study. 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. History of intolerance, allergy, or hypersensitivity to reboxetine or any other ingredient in the study medication. 14. Has a known or suspected history of alcoholism or drug abuse or misuse within 6 months of Screening. 15. Previously participated in another clinical study or received any investigational drug or device or investigational therapy within 30 days or 5 half-lives, whichever is longer, of Baseline.

TEST PRODUCT, DOSAGE AND MODE OF ADMINISTRATION	Reboxetine [redacted] tablet, oral administration, twice daily [redacted] Tablets will be over-encapsulated for blinding purposes.
REFERENCE PRODUCT, DOSAGE AND MODE OF ADMINISTRATION	Matching placebo capsules, oral
TREATMENT REGIMENS	**Sequence 1:** Period 1 (AXS-12) • Week 1 (Day 1 – Day 7): [redacted] over-encapsulated reboxetine tablet in the morning and [redacted] over-encapsulated reboxetine tablet in the afternoon. • Week 2 (Day 8 – Day 14): If tolerated, increase dose to [redacted] over-encapsulated reboxetine tablets in the morning and [redacted] over-encapsulated reboxetine tablet in the afternoon. • Week 3 (Day 15 – Day 17): [redacted] over-encapsulated reboxetine tablet in the morning • Week 3 (Day 18 – Day 21): No treatment Period 2 (Placebo): • Week 4 (Day 22 – Day 28): One placebo capsule in the morning and one placebo capsule in the afternoon • Week 5 (Day 29 – Day 35): If tolerated, increase dose to two placebo capsules in the morning and one placebo capsule in the afternoon • Week 6 (Day 36 – Day 38): One placebo capsule in the morning • Week 6 (Day 39 – 42): No treatment **Sequence 2:** Period 1 (Placebo) • Week 1 (Day 1 – Day 7): One placebo capsule in the morning and one placebo capsule in the afternoon • Week 2 (Day 8 – Day 14): If tolerated, increase dose to two placebo capsules in the morning and one placebo capsule in the afternoon • Week 3 (Day 15 – Day 17): One placebo capsule in the morning • Week 3 (Day 18 – Day 21): No treatment Period 2 (AXS-12): • Week 4 (Day 22 – Day 28) [redacted] over-encapsulated reboxetine tablet in the morning and [redacted] over-encapsulated reboxetine tablet in the afternoon. • Week 5 (Day 29 – Day 35): If tolerated, increase dose to [redacted] over-encapsulated reboxetine tablets in the morning and [redacted] over-encapsulated reboxetine tablet in the afternoon. • Week 6 (Day 36 – Day 38): [redacted] over-encapsulated reboxetine tablet in the morning • Week 6 (Day 39 – 42): No treatment Over-encapsulated tablets of reboxetine or placebo capsule will be dosed twice daily. The first dose (Day 1) will be taken in the morning at the study site during the baseline visit. [redacted] will be assessed by counting the number of capsules dispensed and returned as compared to the expected capsules to have been consumed. Subjects who report <80% compliance with study drug may be withdrawn from study drug after consultation with the Sponsor.
STUDY DURATION	The duration of participation will be approximately 9 weeks as follows: Screening Period: up to 21 days Treatment Period 1: 3 weeks, including one week of down titration Treatment Period 2: 3 weeks, including one week of down titration

CRITERIA FOR EVALUATION	**Primary Efficacy Variable:** The primary efficacy variable is the frequency of cataplexy attacks as self-reported in the Sleep and Symptom Daily Diary **Primary Endpoint:** The primary efficacy endpoint is the change from Baseline to Week 2 of each treatment period in the frequency of cataplexy attacks as recorded in the Sleep and Symptom Daily Diary. Baseline will be calculated as the mean number of attacks during the 7 days prior to the study visit. [redacted] **Secondary Efficacy Variables:** Secondary efficacy variables will include: • PGI-C • HAM-D • ESS • NSAQ • Ability to Concentrate item of the NSAQ • Safety variables: reports of treatment-emergent adverse events (TEAEs); clinical laboratory test results; vital sign measurements; and physical examination findings.
STATISTICAL METHODS	**Analysis Populations:** The following analysis populations are planned for this study: • Modified Intent-to-Treat (mITT) Population: the mITT is the primary analysis population and will include data from all subjects who receive at least one dose of study medication and provide at least 1 post-dose efficacy assessment. • Safety Population: The Safety Population will include all subjects who receive at least 1 dose of the study medication. Membership in the analysis populations will be determined before unblinding. The primary efficacy endpoint will be the change from Baseline to Week 2 of each treatment period in the number of cataplexy attacks as recorded in the Sleep and Symptom Daily Diary. Details of the statistical analysis will be provided in a Statistical Analysis Plan.
SAMPLE SIZE DETERMINATION	A sample size of 20 subjects was selected based on analysis of published results from a pilot open-label trial of reboxetine in narcoleptic subjects, and analyses of treatment effects of other agents studied in cataplexy.