Document Type: Statistical Analysis Plan

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

ClinicalTrials.gov Identifier: NCT03881852

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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.

AXS-12-201 **Phase 2**

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

Statistical Analysis Plan (SAP)

Sponsor
AXSOME Therapeutics, Inc.

[redacted]

Version 1.01 Nov 12, 2019

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the AXS-12-201 data.

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1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.00	4 Nov 2019	Original
1.01	12 Nov 2019	Section 9.1 – Corrected typographical errors.

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ADR	adverse drug reaction
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
C-SSRS	Columbia – Suicide Severity Rating Scale
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Ham-D	Hamilton Depression Rating Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
ICSD-3	International Classification of Sleep Disorders, Third Edition
IEC	Independent Ethics Committee
IIT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MSLT	Multiple sleep latency test
[redacted]	[redacted]
NSAQ	Narcolepsy Symptom Assessment Questionnaire
PGI-S	Patient Global Impression of Severity
PSG	polysomnography
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization

3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol AXS-12-201, Amendment 2, dated 25 Apr 2019.

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methodologies to be used to analyze the safety and efficacy data from the study.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before the database is locked and treatment codes are unblinded. The approved plan will be used to carry out all analyses for the clinical study report. Deviations, if any, from the approved plan will be noted in the clinical study report.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

The primary objective of the study is 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.

The secondary objectives of the study are to assess the the effect of AXS-12 as compared to placebo on the following measures:

- Epworth Sleepiness Scale (ESS)
- Ability to Concentrate in the Sleep and Symptom Daily Diary
- Number of inadvertent naps or sleep attacks in the Sleep and Symptom Daily Diary
- Individual items of the Narcolepsy Symptom Assessment Questionnaire (NSAQ)
- [redacted]
- Hamilton Rating Scale for Depression (HAM-D)

4.2 STUDY TREATMENTS

In this crossover study all subjects will be randomized in a 1 : 1 ratio to Sequence 1 or Sequence 2. Subjects in Sequence 1 will receive AXS-12 in Period 1 and placebo in Period 2. Subjects in Sequence 2 will receive placebo in Period 1 and AXS-12 in Period 2.

4.3 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 Epworth Sleepiness Scale (ESS), Hamilton Rating Scale for Depression (HAM-D), the Narcolepsy Symptom Assessment Questionnaire (NSAQ), and the Ability to Concentrate item of the NSAQ as assessed in the Sleep and Symptom Daily Diary.

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]

- Week 1 (Day 1 – Day 7): [redacted] over-encapsulated reboxetine tablet in the morning and [redacted] over-encapsulated reboxetine tablet in the afternoon [redacted]
- 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 [redacted]

[redacted] Subjects will be monitored for safety and tolerability at each titration step.

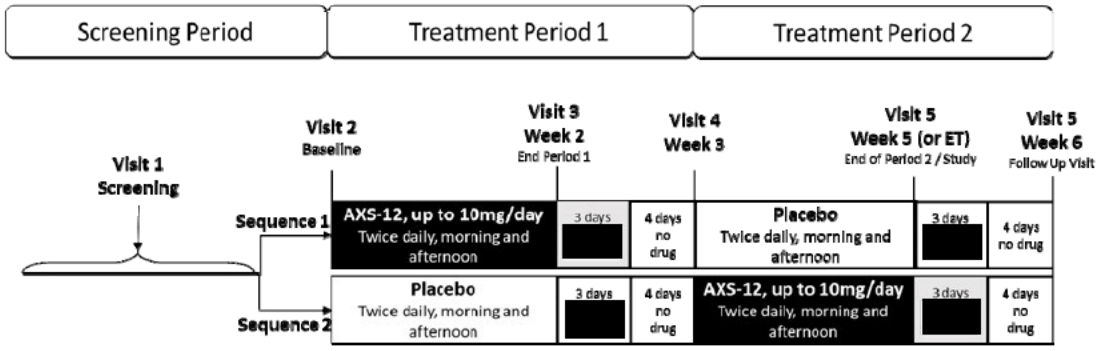
All study medication will be of similar appearance in order to maintain the integrity of the blind.

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

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



4.4 RANDOMIZATION AND BLINDING

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 [redacted]

Detailed blinding and unblinding procedures can be found in the protocol.

5.0 ANALYSIS POPULATIONS

5.1 RANDOMIZED POPULATION

The randomized population will consist of all subjects who complete the Screening Phase and are randomized to a treatment sequence.

5.2 SAFETY POPULATION

The safety population will include all subjects who have received study medication. All safety analyses will use the safety population.

5.3 MODIFED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) population 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-dose efficacy assessment.

5.4 PER PROTOCOL POPULATION

The Per Protocol population will include all subjects in the mITT population with no major protocol violations. Major protocol violation criteria will be established prior to the database lock. Protocol deviations will be presented in the clinical study report. Efficacy analyses may also be performed based on the per protocol population.

6.0 GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed [redacted] and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation, median, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the normal approximation without continuity correction.

Data listings will present all data collected on CRFs by study drug, center, and subject number.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement prior to randomization will be considered the baseline measurement.

6.2 SOFTWARE

[redacted]

6.3 CHANGES TO PLANNED ANALYSES

Draft versions of the SAP will be numbered sequentially as Version 0.0i. The final approved version will be numbered as Version 1.00. Revisions after the "Final" version will be numbered as Version 1.0x. The Clinical Study Report will document any changes made after the final version approved before unblinding.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., mITT, Per Protocol or Safety) in the title.

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment sequence and will include the number of subjects randomized, the number and percentage of randomized subjects in the safety, ITT, and per protocol (if applicable) populations, as well as the number and percentage of subjects who complete the study. The summaries will also include the reasons for early discontinuation from the study.

Disposition summaries will be presented for safety, mITT, and per protocol populations (if applicable) separately.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of demographics and baseline characteristics will be presented by treatment arm and overall for the mITT and safety populations. The demographic characteristics will consist of age, sex, ethnicity, region (US and ex-US), and race using descriptive statistics.

Demographic data including age, race, ethnicity, region, and gender, as well as baseline clinical characteristics will be summarized. Age will be calculated based on the following conditional algorithm:

- Has the patient had his/her birthday this year?
    - Yes, then AGE = (year of informed consent) – (year of birth).
    - No, then AGE = (year of informed consent) – (year of birth) – 1.

Clinical baseline characteristics summarized will include Narcolepsy Disease Related History.

7.3 MEDICAL HISTORY

Medical history will be coded using MedDRA dictionary. A medical history listing will be presented.

8.0 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO DRUG Dictionary Enhanced September 2018. Prior and concomitant medications will be summarized by treatment arm in the safety population by anatomical therapeutic chemical (ATC) Class Level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment component. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment component and no more than 7 days after the last administration of any study treatment component. Medications with start and stop dates that bracket the date of first administration of any study treatment component will be summarized as both prior and concomitant medications.

Medications that were clearly stopped prior to the date of first administration of any study treatment component will be included in the prior medications table, and medications that clearly started on or after the date of first administration of any study treatment component will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

Prior and Concomitant medication will be summarized for the safety population.

9.0 EFFICACY ANALYSES

The number of partial and complete cataplexy attacks, as well as the total number of attacks, are recorded daily. In addition, the rating of the ability to concentrate (1=Very Good, 2=Good, 3=Average, 4=Poor, 5=Very Poor) and the total number of inadvertent naps or sleep attacks are recorded daily. Unless otherwise stated, for these daily captured efficacy variables, the weekly average will be used in the analyses. The weekly average is derived by the average of the non-missing scores captured during the 7 days prior to the given visit. For example, the baseline score will be derived by the average of the non-missing scores captured during the 7 days prior to randomization date.

9.1 PRIMARY EFFICACY VARIABLE

9.1.1 DERIVATION OF PRIMARY EFFICACY VARIABLE

Primary Efficacy Variable
The primary efficacy variable will be the change from baseline in the total number of cataplexy attacks. The change will be calculated as Baseline – Post Baseline. A positive change is indicative of improvement.

9.1.2 PRIMARY ANALYSIS

The changes from baseline in the total number of cataplexy attacks will be analyzed using a Mixed Model. This model will include Sequence (1 or 2), patient, treatment (AXS-12 or placebo), Period as fixed effects and intercept as random. [redacted]

[redacted]

The estimated treatment effects as well as the treatment differences (AXS-12 - Placebo) along with the 95% confidence intervals of the treatment differences will be presented.

The primary endpoint or timepoint will be the overall treatment difference, then Week 2 of the treatment, followed by Week 1 of treatment.

9.1.3 HANDLING OF MISSING VALUES

Missing values will not be imputed.

9.2 SECONDARY EFFICACY OUTCOMES

Secondary endpoints include:

- Changes from Baseline (Baseline – Post Baseline) in the total number of inadvertent naps or sleep attacks in the daily diary. [redacted]
- Changes from Baseline (Baseline – Post Baseline) in the rating of the ability to concentrate in the daily diary. [redacted]
- Patient Global Impression of Change (PGI-C) for cataplexy. [redacted] The frequency counts of categories will also be presented.
- Changes from Baseline (Baseline – Post Baseline) in the Hamilton Depression Rating Scale (HAM-D). [redacted]
- Changes from Baseline (Baseline – Post Baseline) in the Epworth Sleepiness Scale (ESS) score. [redacted]
- Narcolepsy Symptom Assessment Questionnaire (NSAQ).
    - Number of cataplexy attacks, Number of hypnagogic hallucinations, Number of sleep paralysis episodes, Number of inadvertent naps or sleep attacks during the day, Number of awakenings at night, Severity of daytime sleepiness: [redacted]

- "Quality of sleep at night", "Ability to concentrate", and "Overall, compared to my condition prior to starting on this experimental medicine, I am presently":

[redacted]

9.3 INTERIM ANALYSES

No interim analyses are planned.

9.4 ADJUSTMENTS FOR MULTIPLICITY

This study has one primary efficacy endpoint. Other than the primary endpoint, the purpose of the study with a small sample size is to generate hypotheses rather than to prove hypotheses. No p-value adjustment will be made in hypothesis testing.

9.5 POWER AND SAMPLE SIZE JUSTIFICATION

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.

10.0 SUMMARIES OF MEASURES OF SAFETY

Safety analyses will be performed for the safety population. Safety evaluations will be based on the incidence, severity, relatedness, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, vital signs, and clinical laboratory results. Since patients received both treatments, the AEs will be attributed to the treatment they last received.

Because there is no pre-specified safety outcome defined in terms of AEs, clinically relevant laboratory parameters, or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

10.1 EXTENT OF EXPOSURE

Summary statistics of exposure to study drug will be tabulated by treatment group, and by duration (in days) of exposure. The duration will be calculated as last dosing date – first dosing date + 1.

10.2 ADVERSE EVENTS

Each AE and serious adverse event (SAE) term recorded on the case report forms (CRFs) by primary system organ class (SOC) will be mapped to a preferred term using the MedDRA dictionary. The investigator will assess AE severity and relationship to the study treatment.

A treatment emergent adverse event (TEAE) is defined as any AE that occurs within the TEAE window. This window starts on the randomization date and ends 7 days after the last dosing date for non-serious AEs and 30 days after the last dosing for SAEs. All AEs that are considered by the Investigator as treatment related will be treated as TEAEs. Only TEAEs will be summarized in tables (unless otherwise stated AEs in tables are TEAEs). However, all AEs recorded will be listed. For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix B.

AEs will be summarized by the number and percent of subjects in each primary SOC and preferred term. Patients will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and severity will be provided. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the event with the highest severity. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest severity. AEs by primary SOC, preferred term and relationship to study drug will be provided as well. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the most related event. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that primary SOC category by using the most related event. In addition, SAEs by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per patient.

In the AE summary, preferred terms within each SOC will appear in alphabetical order.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Other safety analyses will be performed as appropriate

10.3 VITAL SIGNS

Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a seated position for at least 5 minutes. Vital sign values will be summarized by sequence and period.

10.4 PHYSICAL EXAM

Number and percent of subjects with abnormal physical exam findings at Screening will be summarized by body system, sequence and overall. Physical Exam data for each subject will also be presented in a listing.

11.0 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Major protocol deviations from entry criteria and treatment compliance will be summarized as far as they can be extracted from numeric or coded study data.

12.0 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and crosscheck of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

13.0 REFERENCES

None

14.0 APPENDICES

14.1 APPENDIX A - LIST OF TABLES, LISTINGS, AND FIGURES

List of Tables, Figures, and Listings will be documented separately.

14.2 APPENDIX B - IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of randomization.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of randomization, then set month and day to month and day of randomization
- If year < year of randomization, then set month and day to December 31.
- If year > year of randomization, then set month and day to January 1.

If month and year are present and day is missing:

- If year=year of randomization and
    - If month = month of randomization then set day to day of first dose
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to first day of month
- If year < year of randomization then set day to last day of month
- If year > year of randomization then set day to first day of month

For all other cases, set onset date to date of randomization.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to randomization, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to randomization, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.
If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.