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Protocol Title: A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects with Major Depressive Disorder

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- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information.
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AXS-05-MDD-201 **Phase II**

A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects with Major Depressive Disorder

Statistical Analysis Plan (SAP)

Sponsor
AXSOME Therapeutics, Inc.
[redacted]

Version 1.00 11 December 2018

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-05-MDD-201 data.

AXSOME Therapeutics, Inc.

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1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.00	11 December 2018	First SAP

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
CGI-I	Clinical Global Impressions–Improvement
CGI-S	Clinical Global Impressions–Severity
CSR	Clinical Study Report
C-SSRS	Columbia - Suicide Severity Rating Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
PT	MedDRA Preferred Term
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self- Rated
SAE	Serious Adverse Event
SOC	MedDRA System Organ Class
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]

3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol AXS-05-MDD-201, Amendment Final Version [redacted].

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 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-05 versus bupropion as measured by MADRS (Montgomery-Åsberg Depression Rating Scale).

The secondary objectives of the study include assessment of the effect of AXS-05 versus bupropion on:

- QIDS-SR-16 (Quick Inventory of Depressive Symptomatology-Self- Rated);
- CGI-I (Clinical Global Impressions–Improvement);
- CGI-S (Clinical Global Impressions–Severity);
- [redacted]
- C-SSRS (Columbia - Suicide Severity Rating Scale); and
- Safety as assessed by AEs, vital signs, and laboratory assessments.

4.2 STUDY TREATMENTS

In this double blind study, subjects will be randomized, in a 1:1 ratio, to one of the following two treatment groups:

Treatment Group	Description
1. AXS-05	105 mg bupropion, 45 mg dextromethorphan tablet, oral
2. Bupropion	Bupropion SR 105 mg matching tablet, oral

4.3 STUDY DESIGN

This study is a randomized, double-blind, active-controlled, Phase 2 trial, consisting of a screening period of up to 4 weeks, and a 6-week treatment period.

Screening Period

Prior to randomization, all subjects will enter an up to four-week screening period (Screening) to determine eligibility. Eligible subjects must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features, based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version (SCID-5-CT), with a current major depressive episode of at least 4 weeks in duration. Eligible subjects must meet all other inclusion and no exclusion criteria.

Treatment Period

Randomization

Subjects who successfully complete Screening will be randomly assigned at the baseline visit (Baseline) to receive either AXS-05 or bupropion sustained release (SR) in a 1:1 ratio for 6 weeks. The randomization schedule will be computer-generated using a permuted block algorithm that will randomly allocate the study drug to randomization numbers.

The study will evaluate only subjects whose diagnosis of MDD with a current major depressive episode of moderate or greater severity is confirmed by an independent assessor based on clinical review [redacted]. However, to maintain the blinding of the study investigators, all subjects will be randomized to receive study medication and be included in the safety analysis.

Treatments

Doses will be titrated as follows:

- Days 1 - 3
  - AXS-05 group: 105 mg bupropion, 45 mg dextromethorphan QD
  - Bupropion group: 105 mg bupropion QD
- Days 4 - 42
  - AXS-05 group: 105 mg bupropion, 45 mg dextromethorphan BID
  - Bupropion group: 105 mg bupropion BID

All QD doses will be taken in the morning, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All BID doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All study drug is of identical appearance and similar weight in order to maintain the integrity of the blind.

Assessments and Visits

Study visits will occur at Screening (Visit 1), Baseline (Day 0, Visit 2), and on Days 3, 7, 14, 21, 28, 42 and 49 (Visits 3 – 9). Study procedures and assessments will be performed during study visits as outlined in the Schedule of Assessments. Visit 3 (Day 3) will be conducted telephonically. Subjects will be reminded during Visit 3 to begin BID dosing on Day 4. All subjects completing 6 weeks of treatment or subjects prematurely discontinuing from the study will be required to complete a follow-up visit one week after the last dose of study drug, Visit 9, telephonically. Assessments will include safety parameters,

MADRS, QIDS-SR-16, CGI-S and CGI-I. [redacted]

[redacted] Study drug compliance will also be assessed at the 80% level by counting the number of tablets dispensed and returned. Noncompliant subjects are subject to early termination from the study.

Details of study design, including the schedule of all assessments, can be found in the protocol.

4.4 RANDOMIZATION AND BLINDING

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 1:1 ratio to AXS-05 or to bupropion. The randomization schedule will be computer generated using a permuted block algorithm that will randomly allocate the study drug to randomization numbers.

No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into this study more than once.

Detailed blinding and unblinding procedures can be found in Section 8.7 of 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 arm.

5.2 SAFETY POPULATION

The safety population will include all subjects who have received study medication. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.

5.3 MODIFIED INTENT-TO-TREAT POPULATION

Based on [redacted] the Modified Intent-to-Treat (mITT) population will consist of all subjects with a diagnosis of MDD and a current major depressive episode of moderate or greater severity, confirmed by an independent assessor, who are randomized, subsequently take at least 1 dose of the study drug, and have at least 1 post-Baseline assessment. The efficacy analysis will be based on this mITT population.

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 using [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. Unless otherwise stated, data will be presented by treatment and subject within treatment.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement on the date of randomization will be considered the baseline measurement. If multiple observations are made during baseline, the baseline will be defined as average of the observations obtained during the baseline phase.

6.2 SOFTWARE

Most analyses will be conducted using [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, safety or Per Protocol) in the title.

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment arm and will include the number of subjects randomized, the number and percentage of randomized subjects in the safety, mITT, 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, Intent-to-Treat, 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, 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.

7.3 MEDICAL HISTORY

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 March 2014. 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 30 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 clearly stopped prior to 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 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 medications will be summarized for the safety population.

9.0 EFFICACY ANALYSES

9.1 PRIMARY EFFICACY VARIABLE: CHANGE FROM BASELINE IN MADRS

9.1.1 DERIVATION OF PRIMARY EFFICACY VARIABLE

The primary efficacy variable will be derived based on MADRS (Montgomery-Åsberg Depression Rating Scale). The changes from baseline will be calculated as baseline – post baseline, therefore, the positive changes are indicative of improvement. Missing values will be imputed via last observation carried forward (LOCF) method.

9.1.2 PRIMARY ANALYSIS

Changes from baseline in MADRS will be analyzed using a Mixed Model with Repeated Measures (MMRM). This analysis of covariance mixed-effect model for repeated measures will include treatment (two levels: 1 indicating active treatment and 2 indicating the control), week (5 levels: Weeks 1 through 4 and Week 6), and treatment-by-week interaction as factors, baseline value as a covariate, and subject as a random effect. SAS default covariance structure (variance components) will be assumed. The MMRM with maximum likelihood estimation will utilize the following pseudo- SAS code for analysis:

The primary hypothesis testing will be overall treatment effects. However, for completeness treatment difference at each post baseline week will also be presented. Overall treatment effects, treatment effects at individual post baseline week, and the differences between treatment effects will be estimated using the least-square mean estimates and will be reported together with the 2-sided 95% confidence interval of the treatment differences.

9.1.3 HANDLING OF MISSING VALUES

Unless otherwise stated, missing values will be imputed via the LOCF method.

9.2 SECONDARY EFFICACY OUTCOMES

The secondary objectives of the study are to assess the effect of AXS-05 versus bupropion on (based on mITT population unless otherwise stated):

1. Change from baseline in QIDS-SR-16 (Quick Inventory of Depressive Symptomatology-Self-Rated);
2. CGI-I (Clinical Global Impressions–Improvement);
3. Change from baseline in CGI-S (Clinical Global Impressions–Severity);

4. [redacted]
5. Percentage of responders on MADRS (response defined as ≥ 50% reduction from baseline)
6. Percentage of responders on MADRS (response defined as ≥ 30% reduction from baseline)
7. Percentage achieving remission on MADRS (remission defined as MADRS ≤ 10)
8. Percentage achieving remission on MADRS (remission defined as MADRS ≤ 12)
9. Overall treatment effects on change from baseline in MADRS (weeks 1-2, weeks 1-3, weeks 1-4, weeks 4-6)
10. Change from baseline on item 1 (apparent sadness) of MADRS
11. Change from baseline in MADRS-6 (MADRS 6-item subscale)
12. Overall treatment effects on change from baseline in MADRS-6 (weeks 1-2, weeks 1-3, weeks 1-4, weeks 4-6)
13. Percentage of responders on MADRS-6 (response defined as ≥ 50% reduction from baseline)
14. Percentage of responders on MADRS-6 (response defined as ≥ 30% reduction from baseline)
15. Overall treatment effects on change from baseline in QIDS-SR-16 (weeks 1-2, weeks 1-3, weeks 1-4, weeks 4-6)
16. Percentage of responders on QIDS-SR-16 (response defined as ≥ 50% reduction from baseline)
17. Percentage of responders on QIDS-SR-16 (response defined as ≥ 30% reduction from baseline)
18. Percentage achieving remission on QIDS-SR-16 (remission defined as QIDS-SR-16 ≤ 6)
19. Percentage achieving remission on QIDS-SR-16 (remission defined as QIDS-SR-16 ≤ 5)
20. Overall treatment effects on change from baseline in [redacted] (week 1, weeks 1-2, weeks 1-3, weeks 1-4, weeks 4-6)
21. Percentage of responders on [redacted] (response defined as ≥ 50% reduction from baseline)
22. Percentage of responders on [redacted] (response defined as ≥ 30% reduction from baseline)
23. Time to clinically meaningful improvement on MADRS (reduction from baseline of ≥ 2); QIDS-SR-16 (reduction from baseline of ≥ 10%, ≥ 20%); [redacted] MADRS-6 (reduction from baseline of ≥ 10%, ≥ 20%)
24. Time to clinical improvement based on the CGI-I (score of 3 [minimally improved] or less)
25. Treatment effects in patients with severe depression based on MADRS (defined as MADRS ≥ 30, ≥ 35); severe or very severe depression based on QIDS-SR-16 (defined as QIDS-SR-16 ≥ 16)
26. Treatment effects based on MADRS in patients who had ≥1 prior antidepressant treatments during the current major depressive episode
27. [redacted]
28. [redacted]

Efficacy variables related to change from baseline will be analyzed via the methods outlined in the analysis for the primary efficacy variable.

CGI-I (Clinical Global Impression Scale-Improvement) is a 7-point scale (1= Very Much Improved and 7= Very Much Worse), and will be analyzed using Cochran-Mantel-Haenszel test using score=ridit option. Frequency of the categories will also be presented.

9.3 INTERIM ANALYSES

No interim analysis is planned.

9.4 ADJUSTMENTS FOR MULTIPLICITY

As this study is a Phase 2 study with a small sample size no p-value adjustments will be made.

9.5 POWER AND SAMPLE SIZE JUSTIFICATION

Approximately 60 subjects (30 per arm) whose diagnosis of MDD with a current major depressive episode of moderate or greater severity is confirmed by an independent assessor based on clinical review [redacted] will be included in the analyses. The sample size was determined based on prior reported experience with trials of a similar stage, in a similar patient population, with a similar objective.

A sufficient number of subjects will be screened to achieve the planned number of subjects.

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. Safety variables will be tabulated and presented by study drug actually 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.

C-SSRS (Columbia - Suicide Severity Rating Scale) will be summarized as a safety assessment.

10.1 EXTENT OF EXPOSURE

Summary statistics of exposure to study drug will be tabulated by treatment group, and by duration.

10.2 ADVERSE EVENTS

Each AE and 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 with an onset date on or after date of randomization, or any ongoing event on the date of first dose that worsens in severity after date of randomization. Only non-serious TEAEs with an onset date prior to date of last dose and serious TEAEs

with an onset date prior to date of the final visit + 30 days will be tabulated in summary tables. However, all AEs recorded will be listed. For the purpose calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

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, serious adverse events (SAE) 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 as well as in decreasing order of total incidence.

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

Other safety analyses will be performed as appropriate

10.3 LABORATORY ASSESSMENTS

Chemistry and Hematology, Urinalysis and Coagulation Profile will be assessed at Screening and Week 6. Summary statistics for these parameters will be presented by visit for the actual value and change from baseline for each test in each laboratory category (Hematology, Chemistry, Urinalysis, and Coagulation Profile). Shift tables will be presented for shifts from baseline lab categories to end of study laboratory category. The three laboratory categories will be: L (below lower bound of normal range), N (within normal range), and H (above higher bound of normal range).

If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the first evaluation at that time point will be used for summarization purposes. For the purpose of determining baseline, the last nonmissing observation on or prior to randomization will be used. The Week 6 values will be the last post-baseline value on or prior to Week 6.

10.4 VITAL SIGNS

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min), collected while sitting, following a rest period of at least 3

minutes. Vital sign values and change from baseline in the vital signs will be summarized for each treatment group.

10.5 PHYSICAL EXAM

Number and percent of subjects with abnormal physical exam findings at Screening will be summarized by body system for each treatment group 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 cross check 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

14.0 APPENDICES

14.1 APPENDIX A - 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.