Document Type: Protocol

Protocol Title: An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Treatment Resistant Depression

ClinicalTrials.gov Identifier: NCT04634669

Document Date: November 8, 2021

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:

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- Proprietary information, such as scales or coding systems, which are considered confidential information.
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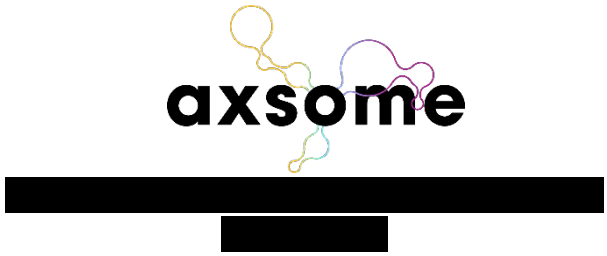
PROTOCOL

COMPOUND NAME/NUMBER:	AXS-05
PROTOCOL NUMBER:	AXS-05-TRD-202
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Treatment Resistant Depression
PROTOCOL VERSION:	Amendment 2
PROTOCOL DATE:	November 8, 2021



[redacted]

This study will be performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Axsome Therapeutics, Inc.

APPROVAL SIGNATURES

PROTOCOL NUMBER:	AXS-05-TRD-202
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety and Efficacy ofAXS-05 in Subjects with Treatment Resistant Depression
Protocol Version:	Amendment 2: November 8, 2021

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

Study Contact and Details

SPONSORED BY:	Axsome Therapeutics, Inc. [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
INVESTIGATORS:	A current list of clinical investigators will be maintained in the TrialMaster File (TMF)

1. SYNOPSIS

Product Name/ Number	AXS-05 (dextromethorphan hydrobromide monohydrate and bupropion hydrochloride)
Protocol Number	AXS-05-TRD-202
Protocol Title	An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Treatment Resistant Depression
Indication	Treatment of Treatment Resistant Depression (TRD)
Development Phase	2
Objective	The primary objective of this study is to evaluate the long-term safety of AXS-05 forthe treatment of TRD. The secondary objective of this study is to evaluate the long-term clinical outcomes of AXS-05 in the treatment of TRD.
Study Design	This study is a multi-center, open-label trial to evaluate the long-term safety and efficacy of AXS-05 in subjects with treatment resistant depression (TRD). Eligible subjects must have either completed Study AXS-05-TRD-201 immediately prior to enrollment in this study or meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depressive disorder (MDD) without psychotic features. Subjects who meet the eligibility criteria will receive AXS-05 [redacted] twice daily for up to 15 months. Subjects will return to the clinic every week for 2 weeks, then every 2 weeks for the next 6 weeks, then monthly thereafter (Months 3-15). At all visits, subjects will be assessed for safety by adverse events (AEs), vital signs, and the Columbia - Suicide Severity Rating Scale (C-SSRS). At Visit 1, and at Months 3, 6, 9, 12 and 15, clinical laboratory examinations, electrocardiograms (EGCs), and physical examinations will also be performed. Patient- and clinician-reported assessments including the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity (CGI-S), Hamilton Anxiety Scale (HAM-A), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) and the Sheehan Disability Scale (SDS) will be assessed at Visit 1, Week 1, Week2, Week 4, Week 6, and Months 2, 3, 6, 9, 12 and 15. The Clinical Global Impression of Improvement (CGI-I) will be assessed at Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, 12 and 15. [redacted]
Planned Number of Subjects	This study will enroll approximately 150 subjects.
Study Centers	Approximately 25 U.S. study centers.
Diagnosis and Subject Selection Criteria -Inclusion Criteria -Exclusion Criteria	**Inclusion Criteria**: A subject will be eligible for participation if all of the following criteria are met: 1. Male or female outpatients, 18 to 65 years of age, inclusive. Subjects who participated in Study AXS-05-TRD-201 eligible regardless of age at entry into this study. 2. Completed Study AXS-05-TRD-201 OR currently meets the DSM-5 criteria for MDD without psychotic features 3. Provides written informed consent to participate in the study, is able to understand the procedures and study requirements, and agrees to abide by the study restrictions and return for the required study assessments. 4. If female and of childbearing potential, has a negative urine pregnancy test result at Visit 1, is practicing at least two adequate methods of birth control (i.e., oral or parenteral contraceptives, intrauterine device, condoms, spermicides), and is not currently pregnant or breastfeeding nor plans to become pregnant during the course of the study. a. Long-term abstinence is acceptable when it is in line with the subjects preferred and usual

lifestyle.

b. Female subjects using a hormonal contraceptive or intrauterine device must have been doing so for at least 1 month before Screening and must follow that product's package insert instructions including additional protection at times when hormonal contraceptive doses might be missed.
c. Female subjects may be enrolled without a negative urine pregnancy test if they are surgically sterile or at least 2 years post-menopausal.
d. Male subjects and their female sexual partners should use an acceptable method of birth control (as noted above) during the study.

Subjects who did not participate in Study AXS-05-TRD-201 must also meet the following criteria:

[redacted]

6. Have been treated with at least 1 prior ADT in the current major depressive episode.
7. Male or female outpatients, 18 to 65 years of age, inclusive.

Exclusion Criteria:

A subject will be excluded from the study if the subject meets any of the following criteria:

1. History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or 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).
2. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure for AXS-05 tablets), to be an unsuitable candidate to receive AXS-05.
3. If the subject is currently receiving or plans to use drugs with known bupropion interactions (as listed in the Wellbutrin SR package insert), Principal Investigator is aware of any potential drug interaction and has deemed the subject acceptable to participate.
4. Any current or recent medical, psychiatric, or social condition that, in the investigator's opinion, is likely to interfere with the conduct of the study, confounds the interpretation of study results, or endangers the subject's well-being. This includes (but is not limited to) any clinically significant oncologic, hematologic, endocrine/metabolic, cardiovascular, respiratory, renal, hepatic, gastrointestinal, infectious or neurologic disease or has a chronic disease which is unstable or progressive.
5. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g., codeine), or any other ingredient in the study medication.
6. History of intolerance to bupropion or dextromethorphan.
7. Unable or unlikely to comply with the study protocol or unsuitable for any other reason, including other conditions that might indicate that the subject is unsuitable for the study as judged by the investigator such as known history of poor medication compliance or significant instability in status of psychosocial issues.
8. Previously received treatment with any investigational drug (other than AXS-05) or device within 30 days of Visit 1.

Test Product, Dosage, and Mode of Administration	AXS-05 (45 mg dextromethorphan HBr, 105 mg bupropion HCl) tablet, oral
Treatment Regimen	[redacted] Twice daily doses should be taken at least 8 hours apart, orally.
Study Duration	The duration of participation will be up to 15 months.
Criteria for Evaluation	**Primary Safety Measures:** • Incidence of treatment-emergent AEs (TEAEs) following dosing with AXS-05. **Additional Safety Measures:** • Change in vital signs (blood pressure and heart rate) over time • Change in ECG findings over time • Change in clinical laboratory measures over time • Incidence of suicidal behavior, as identified via the C-SSRS **Efficacy Measures:** • Change in MADRS over time • CGI-S • CGI-I • Change in HAM-A over time • Change in CPFQ over time • Change in Q-LES-Q over time • Change in SDS over time
Statistical Methods	**Analysis Populations:** The following analysis populations are planned for this study: ▪ *Safety Population*—the Safety Population will include all subjects who receive at least 1 dose of the study medication. Descriptive statistics will be used for all variables and all data over time.
Sample Size Determination	This study will enroll approximately 150 subjects. This sample size will allow for an assessmentof the long-term safety and efficacy in patients with TRD.

SCHEDULE OF ASSESSMENTS

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19 / ETV
Study Day/Week	**D1[f]**	**Wk 1 (± 2d)**	**Wk 2 (± 2d)**	**Wk 4 (± 3d)**	**Wk 6 (± 3d)**	**Mo 2 (± 7d)**	**Mo 3 (± 7d)**	**Mo 4 (± 7d)**	**Mo 5 (± 7d)**	**Mo 6 (± 7d)**	**Mo 7 (± 7d)**	**Mo 8 (± 7d)**	**Mo 9 (± 7d)**	**Mo 10 (± 7d)**	**Mo 11 (± 7d)**	**Mo 12 (± 7d)**	**Mo 13 (± 7d)**	**Mo 14 (± 7d)**	**Mo 15 (± 7d)**
Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Physical Examination	X*						X			X			X			X			X
ECG[d]	X*						X			X			X			X			X
Serum Chemistry	X*						X			X			X			X			X
Vital Signs, Height/Weight[a]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[b]	X*			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
MADRS	X*	X	X	X	X	X	X			X			X			X			X
CGI-I		X	X	X	X	X	X			X			X			X			X
CGI-S	X*	X	X	X	X	X	X			X			X			X			X
HAM-A	X	X	X	X	X	X	X			X			X			X			X
CPFQ	X	X	X	X	X	X	X			X			X			X			X
Q-LES-Q	X	X	X	X	X	X	X			X			X			X			X
SDS	X	X	X	X	X	X	X			X			X			X			X
C-SSRS	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensation[c]	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Conducted as part of the End of Study (EOS) visit during Study AXS-05-TRD-201

Abbreviations: C-SSRS = Columbia - Suicide Severity Rating Scale; CGI-I =Clinical Global Impression of Improvement; CGI-S =Clinical Global Impression of Severity; D = day; CPFQ =Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; ECG = electrocardiogram; ETV = early termination visit; HAM-A = Hamilton Anxiety Scale; MADRS =Montgomery-Åsberg Depression Rating Scale; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS = Sheehan Disability Scale; Wk = week.

a Vital signs, including blood pressure, pulse, respiratory rate, and oral body temperature, will be measured after the subject has been in a seated position for at least 5 minutes. Weight willbe measured at each visit and height will only be measured at Visit 1.

b Required only for females of childbearing potential.c
Study drug can be re-dispensed, when appropriate.

d Subjects should rest in the supine position for at least 2 minutes prior to performing ECG.

[redacted]

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Class
AUC	Area Under the Curve
AXS	Axsome Therapeutics
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BUP	Bupropion
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement of Illness
CNS	Central Nervous System
CPFQ	Cognitive and Physical Functioning Questionnaire
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia – Suicide Severity Rating Scale
DM	Dextromethorphan
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAM-A	Hamilton Anxiety Scale
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
LLC	Limited Liability Company
LLN	Lower Limit of Normal
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat Population
NMDA	N-methyl-D-aspartate
OTC	Over-the-Counter

PK	Pharmacokinetic
QD	Once daily
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDS	Sheehan Disability Scale
SOC	System Organ Class
SOP	Standard Operating Procedure
SR	Sustained Release
TEAE	Treatment-Emergent Adverse Events
TMF	Trial Master File
U.S.	United States
UADR	Unexpected Adverse Drug Reaction
UAE	Unexpected Adverse Event
ULN	Upper Limit of Normal
USA	United States of America
WHO	World Health Organization

4. INTRODUCTION

4.1. Background

AXS-05 is a novel, oral, investigational drug product under development for the treatment of central nervous system (CNS) disorders. AXS-05 is a combination of dextromethorphan (DM), an N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, and inhibitor of the serotonin and norepinephrine transporters, and bupropion a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. The rationale for studying AXS-05 for various CNS conditions is based on the multi-modal mechanisms of action.

The clinical utility of DM has been limited by its rapid metabolism through CYP2D6 yielding low plasma levels even at high and repeated doses. As bupropion and its metabolites are inhibitors of CYP2D6, co-administration of bupropion and DM leads to substantially increased DM plasma concentrations. In three Phase 1 pharmacokinetic trials of AXS-05, administration of bupropion in combination with DM resulted in a significant increase in DM exposure (C_{max} and AUC) at all doses tested (AXS-05 Investigator's Brochure). Administration of bupropion (ranging from 150 mg to 300 mg per day) and DM (ranging from 60 mg to 120 mg per day) resulted in C_{max} and AUC_{0-12} of DM on Day 8 that were 20 to 27 times and 30 to 36 times, respectively, the values observed on Day 1 of dosing. DM exposure increased in a dose-dependent manner with increasing doses of both DM and bupropion. Administration of DM did not appear to affect the pharmacokinetics of bupropion. There was no significant difference in the rates or types of adverse events (AEs) in the combination groups as compared to a group receiving bupropion alone. The positivepharmacokinetic interaction between bupropion and DM therefore enables DM's clinical utility intreating depression by increasing DM's plasma levels into a potentially therapeutic range.

4.2. Clinical Development of AXS-05

AXS-05 is currently in development for the treatment of major depressive disorder (MDD), treatment resistant depression (TRD), agitation associated with Alzheimer's disease, and smoking cessation. The dose of AXS-05 used in these trials has been 45 mg DM HBr / 105 mg bupropion HCl, which is the dose utilized in the clinical development program. To date over 1000 patients have received this dose of AXS-05 from durations of one day to more than 6 months.

Brief summaries of the completed clinical trials are described below.

4.2.1. Completed Studies in Major Depressive Disorder

Axsome has completed two efficacy trials of AXS-05 in MDD, which are intended to support marketing authorization of the product. In both studies, AXS-05, at a dose of 45 mg DM HBr and 105 mg bupropion HCl, dosed twice daily, demonstrated a statistically significant, substantial and rapid reduction in depressive symptoms versus control. Further data supportive of the efficacy of AXS-05 has been demonstrated in one study in patients with TRD.

<u>Phase 2 Trial of AXS-05 in MDD (Study AXS-05-MDD-201)</u>

Study AXS-05-MDD-201, was a Phase 2 randomized, double-blind, active-controlled, multi-center, trial in which 80 adult subjects with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were treated either with AXS-05 (45 mg DM HBr / 105 mg bupropion HCl) (n=43), or the active comparator bupropion (105 mg) (n=37), twice daily for 6 weeks. The primary endpoint of the study was the change from baseline in the Montgomery

Åsberg Depression Rating Scale (MADRS) total score, calculated at each time point in the study and averaged (overall treatment effect).

Treatment with AXS-05 resulted in a substantial, rapid, and statistically significant reduction in depressive symptoms as compared to the active comparator bupropion. On the primary endpoint, AXS-05 was associated with a statistically significant average mean reduction from baseline in the MADRS total score over the 6-week treatment period of 13.7 points for AXS-05 compared to 8.8 for bupropion ($p<0.001$). At Week 6, AXS-05 was associated with a mean reduction from baseline in the MADRS total score of 17.2 points compared to a reduction of 12.1 points for bupropion ($p=0.013$). Remission, prospectively defined as a MADRS total score of ≤ 10, was seen at Week 6 in 47% of patients who received AXS-05, compared to 16% of patients who received bupropion ($p=0.004$). AXS-05 was superior to bupropion on multiple other prespecified secondary endpoints, with statistically significant effects demonstrated on most, including the MADRS-6, Clinical Global Impression of Improvement (CGI-I), and Clinical Global Impression of Severity (CGI-S).

AXS-05 was safe and well tolerated with no reported serious adverse events (SAEs). The most commonly reported AEs in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. Overall, rates of AEs were similar between AXS-05 and bupropion. Therewas no meaningful difference between the two treatment arms in discontinuations due to AEs. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, orsexual dysfunction.

Phase 3 Trial of AXS-05 in MDD (Study AXS-05-MDD-301)

Study AXS-05-MDD-301, was a randomized, double-blind, placebo-controlled, multi-center trial, in which 327 adult patients with confirmed moderate to severe MDD were randomized to treatment with either AXS-05 (45 mg DM HBr / 105 mg bupropion HCl) or placebo twice daily for a total of 6 weeks.

AXS-05 met the primary endpoint by demonstrating a highly statistically significant reduction in the MADRS total score compared to placebo at Week 6, with mean reductions from baseline of 16.6 points for AXS-05 and 11.9 points for placebo ($p=0.002$). AXS-05 rapidly and durably improved depressive symptoms as compared to placebo with statistical significance on the MADRS total score demonstrated at Week 1 and at all time points thereafter. Rates of remission from depression (defined as MADRS ≤10) were statistically significantly greater for AXS-05 compared to placebo at Week 2 ($p=0.013$) and at every time point thereafter, being achieved by 39.5% of AXS-05 patients compared to 17.3% of placebo patients at Week 6 ($p<0.001$).

AXS-05 was well tolerated. The most commonly reported AEs in the AXS-05 arm were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. There was one serious adverse event of pancreatitis in the AXS-05 arm. The rates of discontinuation due to AEs were low in both treatment groups (6.2% for AXS-05 and 0.6% for placebo). Treatment with AXS-05 was not associated with psychotomimetic effects or weight gain.

Completed Phase 3 Trial of AXS-05 in TRD (STRIDE, Study AXS-05-301)

Study AXS-05-301 was a Phase 3, randomized, double-blind, active controlled trial to assess the efficacy and safety of AXS-05 in the 312 adult patients with TRD. Eligible patients randomized in a 1:1 ratio to receive treatment with bupropion HCl (150 mg) or AXS-05 (45 mg DM HBr / 105 mg bupropion HCl) twice daily, for 6 weeks.

AXS-05 rapidly and significantly improved symptoms in patients with TRD as measured by MADRS averaged over the entire 6-week treatment period, a key secondary endpoint, with mean reductions of 8.6 for AXS-05 versus 6.7 for bupropion ($p=0.031$). The rapid onset of action with

AXS-05 treatment was demonstrated with statistically significant mean MADRS reductions at Week 1, the earliest time point measured, of 5.2 versus 3.6 respectively for AXS-05 and bupropion (p=0.02), and at Week 2 of 8.0 versus 6.1 respectively for AXS-05 and bupropion (p=0.035), both time points being key secondary endpoints. At Week 6, the primary endpoint, AXS-05 demonstrated a numerically greater improvement in MADRS, with mean reductions of 11.6 for AXS-05 versus 9.4 for bupropion (p=0.117).

AXS-05 was well tolerated in the trial. The most commonly reported AEs in the AXS-05 arm were dizziness and nausea. The rates of discontinuation due to AEs were low in both treatment groups (2.6% for AXS-05 and 1.9% for bupropion). There were 3 SAEs in the AXS-05 arm, consisting of migraine; overdose; and suicidal ideation, which occurredmore than one week after the cessation of treatment. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or sexual dysfunction.

4.3. Purpose and Rationale for this Study

The aim of this study is to evaluate the long-term safety and efficacy of patients with TRD. This study will provide open-label AXS-05 to patients completing Study AXS-05-TRD-201 and to newly enrolled patients with moderate-to-severe MDD [redacted] and who have received at least 1 antidepressant treatment (ADT) in the current major depressive episode.

5. OBJECTIVES

5.1. Primary Objective

To evaluate the long-term safety of AXS-05 in the treatment of TRD.

5.2. Secondary Objectives

To evaluate the long-term clinical outcomes of AXS-05 in the treatment of TRD.

6. STUDY DESIGN

6.1. Overall Study Design and Plan

This study is a multi-center, open-label trial to evaluate the long-term safety and efficacy of AXS-05 in subjects with treatment resistant depression (TRD). Eligible subjects must have either completed Study AXS-05-TRD-201 immediately prior to enrollment in this study or meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features. Subjects who meet the eligibility criteria will receive AXS-05 [redacted] twice daily for up to 15 months. Subjects will return to clinic every week for 2 weeks, then every 2 weeks for the first 2 months, then monthly thereafter (Months 3-15). At all visits, subjects will be assessed for safety by AEs, vital signs, and the Columbia - Suicide Severity Rating Scale (C-SSRS). At Visit 1, and at Months 3, 6, 9, 12, and 15, clinical laboratory examinations, electrocardiograms (EGCs), and physical examinations will also be performed. Patient- and clinician-reported assessments including the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity (CGI-S), Hamilton Anxiety Scale (HAM-A), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) and the Sheehan Disability Scale (SDS) will be assessed at Visit 1, Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, 12, and 15. The Clinical Global Impression of Improvement (CGI-I) will be assessed at Week 1, Week 2, Week 4, Week 6, and Months 2, 3, 6, 9, 12, and 15.

[redacted]

6.2. Discussion of Study Design

An open-label design is appropriate for assessing the long-term safety of AXS-05 for the treatment of TRD.

6.3. Study Sites

The study will take place at up to approximately 25 study sites in the United States.

6.4. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of the subject, and whom to contact in case of study-related injury. This information will be provided in the subject information and informed consent form (ICF).

7. SUBJECT POPULATION

7.1. Selection of Study Population and Diagnosis

Eligible subjects will meet the below listed eligibility criteria.

7.2. Study Entry Criteria

7.2.1. Inclusion Criteria

A subject will be eligible for participation if all of the following criteria are met:

1. Male or female outpatients, 18 to 65 years of age, inclusive. Subjects who participated in Study AXS-05-TRD-201 eligible regardless of age at entry into this study.
2. Completed Study AXS-05-TRD-201 OR currently meets the DSM-5 criteria for MDD without psychotic features.
3. Provides written informed consent to participate in the study, is able to understand the procedures and study requirements, and agrees to abide by the study restrictions and return for the required study assessments.
4. If female and of childbearing potential, has a negative urine pregnancy test result at Visit 1, is practicing at least two adequate methods of birth control (i.e., oral or parenteral contraceptives, intrauterine device, condoms, spermicides), and is not currently pregnant or breastfeeding nor plans to become pregnant during the course of the study.
    a. Long-term abstinence is acceptable when it is in line with the subjects preferred and usual lifestyle.
    b. Female subjects using a hormonal contraceptive or intrauterine device must have been doing so for at least 1 month before Screening and must follow that product's package insert instructions including additional protection at times when hormonal contraceptive doses might be missed.
    c. Female subjects may be enrolled without a negative urine pregnancy test if they are surgically sterile or at least 2 years post-menopausal.
    d. Male subjects and their female sexual partners should use an acceptable method of birth control (as noted above) during the study.

Subjects who did not participate in Study AXS-05-TRD-201 must also meet the following criteria:

5. [redacted]
6. Have been treated with at least 1 prior ADT in the current major depressive episode.
7. Male or female outpatients, 18 to 65 years of age, inclusive.

7.2.2. Exclusion Criteria

A subject will be excluded from the study if the subject meets any of the following criteria:

1. History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or 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).
2. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure for AXS-05 tablets), to be an unsuitable candidate to receive AXS-05.
3. If the subject is currently receiving or plans to use drugs with known bupropion interactions (as listed in the Wellbutrin SR package insert), Principal Investigator is aware of any potential drug interaction and has deemed the subject acceptable to participate.
4. Any current or recent medical, psychiatric, or social condition that, in the investigator's opinion, is likely to interfere with the conduct of the study, confounds the interpretation of study results, or endangers the subject's well-being. This includes (but is not limited to) any clinically significant oncologic, hematologic, endocrine/metabolic, cardiovascular, respiratory, renal, hepatic, gastrointestinal, infectious or neurologic disease or has a chronic disease which is unstable or progressive.
5. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g., codeine, etc.), or any other ingredient in the study medication.
6. History of intolerance to bupropion or dextromethorphan.
7. Unable or unlikely to comply with the study protocol or unsuitable for any other reason, including other conditions that might indicate that the subject is unsuitable for the study as judged by the investigator such as known history of poor medication compliance or significant instability in status of psychosocial issues.
8. Previously received treatment with any investigational drug (other than AXS-05) or device within 30 days of Visit 1.

7.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. The investigator or designee must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to evaluate the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented,reported, and followed as described in Section 10.2.

Axsome reserves the right to request the withdrawal of a subject because of protocol violations or other reasons.

The investigator also has the right to withdraw subjects from the study or discontinue study drug treatment at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn or discontinues treatment before completing the study, the reason and the date of discontinuation will be recorded on the appropriate electronic case report form (eCRF). If the subject received study drug prior to discontinuation, all attempts should be made to complete the end of study evaluations.

7.4. Subject Replacement Criteria

Subjects who are withdrawn will not be replaced. If a substantial number of subjects are withdrawn from the study, then Axsome will evaluate the need for developing replacement criteria.

8. TREATMENTS

8.1. Identification of Investigational Product

The following study medications will be provided:

- **AXS-05**: a tablet consisting of 45 mg dextromethorphan hydrobromide monohydrate and 105 mg bupropion hydrochloride sustained release in the form of a bilayer tablet for oral administration

[redacted]

8.2. Labeling and Packaging

[redacted]

8.2.1. Labeling

The bottles of the study drug will have a label that meets the applicable regulatory requirements and may include the following: subject identifier, dosage strength, lot number, package number, protocol number, specified number of tablets, caution statement, storage, sponsor/manufacturer identification, and dosing instructions.

8.2.2. Packaging

The study drug will be packaged in bottles, which will include 30 tablets.

8.3. Study Medication Administration

Study drug will be dispensed and/or re-dispensed to eligible subjects at each visit.

8.4. Dispensing and Storage

The study drug is to be used exclusively in this clinical study according to the instructions of this protocol. The investigator or designee is responsible for dispensing the study drug according to the dosage scheme and for ensuring its proper storage.

The investigator or designee must confirm the receipt of the study drug. A copy of this receipt must be kept by the investigator or designee and another copy will be stored at Axsome and/or its designee. The study drug will be dispensed and/or re-dispensed to the subject at each visit.

Once study drug has been received on site it must be stored at 25°C (77°F) and in a dry place in a securely locked area that is not generally accessible. Excursions between 15° and 30°C (59° and 86°F) are permitted. The storage area will be accessible only to those persons authorized by the investigator.

8.5. Method of Assigning Subjects to Treatment

This is an open-label study; all subjects will receive AXS-05.

8.6. Blinding and Unblinding Treatment Assignment

Not applicable as this is an open-label study.

8.7. Selection of Doses in the Study

The dose of AXS-05 (45 mg DM HBr, 105 mg bupropion HCl) [redacted] was selected based on the results of pharmacokinetic Phase 1 trials of AXS-05. The selected dose resulted in the targeted plasma concentrations of the components of AXS-05.

8.8. Selection of Timing of Dose for Each Subject

A significant food effect has not been reported for AXS-05; therefore, study drug may be taken with or without food.

The timing of the dose (twice daily) was selected based on the results of the previously completed studies in subjects with depression.

8.9. Dose Adjustment Criteria

Dose adjustment is not allowed during this study.

8.10. Drug Accountability

The investigator, or designee, must maintain adequate records showing the receipt, dosing, or other disposition of the study drug provided, including the date, quantity, batch or code number, and identification of subjects (subject number) who received it. The investigator will not supply the study drug to any person except those named as sub-investigators on the Form FDA 1572, designated study personnel, and subjects in this study. The investigator will not dispense the study drug from any study sites other than those listed on the Form FDA 1572. The study drug may not be relabeled or reassigned for use by other subjects. If any of the study drug is not dispensed; is lost, stolen, spilled, unusable; or is received in a damaged container, this information must be documented and reported to Axsome Therapeutics and appropriate regulatory agencies, as required.

Upon completion of the study, the study drug (unused and empty packaging, e.g., study drug bottles) must be left in the original packaging and returned to Axsome or its designee for destruction.

8.11. Treatment Compliance

Study drug compliance will be closely monitored by counting the number of tablets dispensed and returned.

Subjects will be instructed to bring any unused study drug and empty containers to the clinic at each visit or at the time of early study discontinuation. Before new study drug is dispensed at each visit, every effort will be made to collect the unused study drug to confirm compliance.

Investigators will perform drug accountability of study drug at each visit to determine a subject's usage. Study drug compliance will be assessed at the 80-120% level.

8.12. Prior and Concomitant Therapies

Medication history during the previous 1 year (5 years in the case of psychiatric drug history) will be recorded in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the case report form (CRF).

At each visit, subjects will be queried as to whether or not they have taken any concomitant medications and, if so, the Investigator will record the medications taken and the reasons for their use. All concomitant medications and treatments used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate CRF.

8.13. Prohibited Therapies

The following concomitant medications are not allowed during this study:

- Drugs with known bupropion interactions (as listed in the Wellbutrin SR package insert)
- Drugs containing dextromethorphan or bupropion (other than AXS-05)
- Monoamine oxidase inhibitors (MAOIs)
- Linezolid
- Intravenous methylene blue

Beyond the above listed items, there are no restrictions on concomitant medications during this study.

8.14. Treatment After the End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9. STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Assessments. Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of assessments for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled within the visit window specified below.

9.1. Study Periods, Visits, and Procedures

9.1.1. Visit 1: Enrollment (Day 1)

Subjects entering from Study AXS-05-TRD-201

Day 1 of this study maybe combined with the End of Study (EOS) Visit in Study AXS-05-TRD-201. Subjects will be instructed not to take study drug (from Study AXS-05-TRD-201) on the morning of Visit 1. Any assessments that are required for both studies will be performed once and recorded in the respective CRF for each study. Subjects will sign an ICF before procedures which are specific to this study are performed. Day 1 is the first dose of study drug, which will be used to calculate future visit dates.

Subjects who did not participate in Study AXS-05-TRD-201

Informed consent will be obtained prior to conducting any study-related procedures. Procedures related to eligibility [redacted] should be conducted first to confirm eligibility. Subjects may be enrolled once eligibility is confirmed. In select cases, the Day 1 assessments may be conducted across more than one day, with the official Day 1 study day. Day 1 is the first dose of study drug, which will be used to calculate future visit dates.

The following procedures will be performed at Visit 1:

- Obtain written informed consent.
- Review inclusion/exclusion criteria.
- Confirm demographics, medical history, and concomitant medications
- Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems.
- Conduct 12-Lead ECG after subject has been in the supine position for at least 2 minutes.
- Collect blood sample for serum chemistry analysis.
- Record vital signs (seated blood pressure, pulse, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes and measure height and weight.
- Perform onsite urine pregnancy test for all female subjects of childbearing potential.
- Conduct the following scales:
  - MADRS
  - HAM-A
  - CGI-S
  - CPFQ
  - Q-LES-Q
  - SDS
  - C-SSRS
- Dispense study drug. The first dose should be taken in clinic. Subject should be instructed to take one dose each morning for the next 2 days. On the 4th day of dosing, the subject should begin twice daily dosing.

9.1.2. Visit 2 (Week 1) and Visit 3 (Week 2) (+/- 2 days)

The following procedures will be performed at Visits 2 and 3:

- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Measure weight.
- Conduct the following scales:
  - MADRS
  - HAM-A
  - CGI-S

  - CGI-I
  - CPFQ
  - Q-LES-Q
  - SDS
  - C-SSRS
- Dispense and/or re-dispense study medication.
- Perform drug accountability.
- Record AEs and concomitant medications.

9.1.3. Visit 4 (Week 4) (+/- 3 days)

The following procedures will be performed at Visit 4:

- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Measure weight.
- Perform onsite urine pregnancy test for all female subjects of childbearing potential.
- Conduct the following scales:
  - MADRS
  - HAM-A
  - CGI-S
  - CGI-I
  - CPFQ
  - Q-LES-Q
  - SDS
  - C-SSRS
- Dispense and/or re-dispense study medication.
- Perform drug accountability.
- Record AEs and concomitant medications.

9.1.4. Visit 5 (Week 6) (+/- 3 days)

The following procedures will be performed at Visit 5:

- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Measure weight.
- Conduct the following scales:
  - MADRS [redacted]
  - HAM-A
  - CGI-S

- CGI-I
- CPFQ
- Q-LES-Q
- SDS
- C-SSRS

- Dispense and/or re-dispense study medication.
- Perform drug accountability.
- Record AEs and concomitant medications.

9.1.5. Visits 6 - 18: Months 2 - 14 (+/- 7 days)

The following procedures will be performed at these study visits:

- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Measure weight.
- Perform onsite urine pregnancy test for all female subjects of childbearing potential.
- Dispense and/or re-dispense study medication.
- Record AEs and concomitant medications.
- Perform drug accountability.
- C-SSRS
- **Additionally, at Visit 6, the following will occur:**
  - Conduct the following scales:
    - MADRS
    - HAM-A
    - CGI-S
    - CGI-I
    - CPFQ
    - Q-LES-Q
    - SDS
- **Additionally, at Visits 7, 10, 13, and 16, the following will occur:**
  - Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems. *Brief physical exams may be performed at other study visits in response to subject reported adverse events.*
  - Conduct a 12-Lead ECG after subject has been in the supine position for at least 2 minutes.
  - Collect blood sample for serum chemistry analysis.
  - Conduct the following scales:
    - MADRS
    - HAM-A
    - CGI-S

- CGI-I
- CPFQ
- Q-LES-Q
- SDS

9.1.6. Visits 19 (Month 15), End of Study / Early Termination (+/- 7 days)

The following procedures will be performed at Visit 19 or Early Termination Visit:

- Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems.
- Conduct a 12-Lead ECG after subject has been in the supine position for at least 2 minutes.
- Collect blood sample for serum chemistry analysis.
- Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a seated position for at least 5 minutes.
- Measure weight.
- Perform onsite urine pregnancy test for all female subjects of childbearing potential.
- Conduct the following scales:
  - MADRS
  - HAM-A
  - CGI-S
  - CGI-I
  - CPFQ
  - Q-LES-Q
  - SDS
  - C-SSRS
- Perform drug accountability.
- Record AEs and concomitant medications.

9.1.7. Unscheduled Visits

Unscheduled visits may occur as needed during the study. Examples of reasons for unscheduled visit may include dispensing additional study medication or for safety assessments.

9.2. Study Duration

The study will last up to approximately 15 months for an individual subject.

9.3. Assessments

9.3.1. Efficacy

9.3.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS [1] is a clinician-rated scale. The MADRS is used to assess depressive symptomatology during the previous week. Subjects are rated on 10 items to assess feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty

concentrating and lack of interest. Each item is scored on a 7-point scale. A score of 0 indicates the absence of symptoms, and a score of 6 indicates symptoms of maximum severity.

9.3.1.2. Clinical Global Impression – Improvement (CGI-I)

The CGI-I scale [2] is a clinician-rated scale that is used to rate total improvement or worsening of mental illness regardless of whether the Investigator considers it to be a result of drug treatment or not. The subject is rated on a scale from 1 to 7, with 1 indicating that the subject is very much improved and 7 indicating that the subject is very much worse. The CGI-I will be administered by the Investigator or a Sub-Investigator with extensive professional training and experience in assessing mental illness.

9.3.1.3. Clinical Global Impression – Severity (CGI-S)

The CGI-S scale [2] is a clinician-rated scale used to rate the severity of the subject's current state of mental illness compared with a subject population with TRD. The subject is rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill subjects." The CGI-S will be administered by the Investigator or a Sub-Investigator with extensive professional training and experience in assessing mental illness.

9.3.1.4. Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

The Q-LES-Q-SF [3] is a self-reported questionnaire designed to measure of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. It is a 16-item questionnaire, where each item is scored from 0 (very poor) to 5 (very good). The total raw score is the sum of the first 14-items, ranging from 14 to 70. The raw total score is transformed into a percentage maximum possible score using the following formula: (raw total score − minimum score) / (maximum possible raw score − minimum score).

9.3.1.5. Sheehan Disability Scale (SDS)

The SDS [4] is a 3-item patient-facing questionnaire used to evaluate impairments in the domainsof work, social life/leisure, and family life/home responsibility. All items are rated on an 11-point continuum (0 = no impairment to 10 = most severe).

9.3.1.6. Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A [5] is a clinician-administered scale which consists of 14 items, each rated on a five-point scale ranging from 0 (not present) to 4 (very severe). The highest possible score is 56, which represents the most severe form of anxiety; the lowest possible score is 0, which represents an absence of anxiety.

9.3.1.7. Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

The CPFQ [6] is a 7-item patient-rated scale used to measure cognitive and executive dysfunctionin mood and anxiety disorders and was developed to assess clinically relevant cognitive and physical symptoms that could emerge or persist during long-term treatment for depression. Subjects grade the perceived quality of their physical and cognitive functioning. It is scored from 1-6 with increasing severity that individually evaluates 7 distinct items: motivation/enthusiasm, wakefulness/alertness, energy, focus/attention, recall, ability to find words, and sharpness/mental acuity. The physical dimension of the CPFQ assesses sleepiness and fatigue, and the cognitive dimension assesses apathy, inattention, forgetfulness, word-finding difficulties, and mental slowness.

9.3.2. Clinical Pharmacology

Not applicable for this study.

9.3.3. Safety

Safety assessments will include the evaluation of treatment-emergent adverse events (TEAEs), C-SSRS, clinical laboratory test results, ECGs, vital sign measurements, and physical examination findings.

9.3.3.1. Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 10.

9.3.3.2. Clinical Laboratory Safety Assessments

9.3.3.2.1. Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Assessments.

Serum Chemistry	Albumin, total bilirubin, direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, random glucose, sodium, potassium, and chloride.
Urine Pregnancy Test	For females of childbearing potential subjects. A test will be performed on site at each study visit.

9.3.3.2.2. Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist about theshipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator or designee is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

9.3.3.2.3. Evaluation of Clinical Laboratory Values

The normal ranges of values for clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Axsome before the start of the study. These will be regarded as the reference ranges on which decisions will be made.

If a clinical laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator is responsible for determining whether these occurrences are considered as AEs.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of the treatment must be reported as AEs and followed as described in Section 10.2.5.

All measurements described in this section are recognized standard methods.

9.3.3.3. Clinical Examinations

9.3.3.3.1. Vital Signs

Vital signs will include seated blood pressure, pulse, respiratory rate, and oral body temperature. Blood pressure will be measured after the subject has been in a sitting position for 5 minutes. Height will be collected at Visit 1 and weight will be collected at all study visits.

9.3.3.3.2. Physical Examination

A complete physical examination (excluding breast and genitourinary examination) will be performed at the time points outlined in the Schedule of Assessments.

9.3.3.3.3. Electrocardiogram (ECG)

A 12-lead ECG will be conducted after the subject has been resting (supine) for at least 2 minutes. At a minimum, the following parameters should be collected; PR interval, QRS duration, and QTcF.

The date and time of last dose prior to each ECG will be recorded.

If the subject reports cardiac related adverse events, they should return for unscheduled visits and an ECG should be conducted.

9.3.3.3.4. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS [7] is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

At all visits the C-SSRS will be completed for ideation and behavior with a recall period since the last visit.

The C-SSRS will be administered by the Investigator or designee.

10. ADVERSE EVENTS

10.1. Definitions

10.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

10.1.2. Adverse Drug Reaction

All noxious and unintended responses to a study drug related to any dose should be considered adverse drug reactions (ADRs).

The phrase "related to study drug" means that a causal relationship between a study drug and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a study drug qualify as ADRs.

All AEs for which the judgment of relationship to the study drug is "possible" or higher will be considered ADRs. If a relationship to the study drug is not given, then the AE must be treated as if the relationship to the study drug were "possible."

10.1.3. Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is an event for which the nature or severity is consistent with the known AE profile of the product. For a study drug, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is an event for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected).

10.1.4. Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- Requires inpatient hospitalization or prolongation of existing hospitalization. NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. Anelective hospital admission to treat a condition present before exposure to the study drug, ora hospital admission for a diagnostic evaluation of an AE, <u>does not</u> qualify the condition orevent as an SAE. Further, an overnight stay in the hospital that is only due to transportation,organization, or accommodation problems and without medical background does not need to be considered an SAE.*
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy <u>is</u> an SAE. However, a newly diagnosed pregnancy in a subject who has received a study drug is <u>not</u> considered an SAE unless it is suspected that the study*

drug(s) interacted with a contraceptive method and led to the pregnancy.

- Is an important medical event.
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The occurrence of malignant tumors is also to be considered serious.*

10.1.5. Significant Adverse Events

Other significant AEs are defined events that led to a significant intervention, including significant additional concomitant therapy.

10.1.6. Treatment-Emergent Adverse Events (TEAEs)

An AE is defined as treatment emergent if the first onset or worsening is after an administration of study drug and not more than 7 days after the last dose. Any AEs that are deemed to be treatment related by the investigators will always count as TEAEs. The primary safety assessments will be based on TEAEs. For completeness, a listing of all reported AEs will be presented in the clinical study report (CSR).

10.2. Management of Adverse Events

Adverse events will be collected after administration of study drug through the End of Study (or Early Termination).

10.2.1. Collection of Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

10.2.2. Evaluation of Adverse Events

10.2.2.1. Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 10.1.4.

10.2.2.2. Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 10.1.4.

10.2.2.3. Action(s) Taken

Action(s) taken may consist of:

Dose not changed	An indication that a medication schedule was maintained.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

10.2.2.4. Outcome at the Time of Last Observation

The outcome, including Fatal, at the time of last observation will be classified per eCRFcompletion instructions. Only select fatal as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

10.2.2.5. Adverse Event Relationship to the Study Drug

The investigator will also assess the relationship (if any) between the AE and the study treatment (*not related, unlikely, possibly, probably or definitely).*

The investigator will use the following definitions to classify the relationship of an AE to study drug:

Not related: AEs which, after careful consideration, are clearly and undeniably because of extraneous causes (e.g., disease, environment);

Unlikely: This category can generally be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug. An AE may be considered unlikely to be related if or when at least two of the following criteria are fulfilled:

1) The event does not follow a reasonable temporal sequence from administration of the test drug;
2) The event could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event does not follow a known pattern of response to the test drug;
4) The event does not reappear or worsen when the drug is re-administered.

Possibly: This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if or when at least two of the following criteria are fulfilled:

1) The event follows a reasonable temporal sequence from administration of the drug;
2) The event could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event follows a known pattern of response to the test drug.

Probably: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An AE may be considered probably related if or when least three of the following criteria are fulfilled:

1) The event follows a reasonable temporal sequence from administration of the drug;
2) The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event disappears or decreases on stopping or reducing the dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, but drug-relatedness clearly exists, e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia;
4) The event follows a known pattern of response to the test drug.

Definitely: This category applies to those AEs, which the investigator feels are undeniably related to the test drug. An AE may be assigned an attribution of definitely related if or when all the following criteria are fulfilled:

1) The event follows a reasonable temporal sequence from administration of the drug;
2) The event could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
3) The event disappears or decreases on stopping or reducing the dose and reappears with re-exposure to study drug (Note: this does not mean that the patient is to be re-exposed to study drug, however, a category of definitely related can only be used when recurrence is observed);
4) The event follows a known pattern of response to the test drug.

10.2.3. Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information, where appropriate (the period of observation for the study is described in Section 10.2.):

- AE name or term.
- When the AE first occurred (start date).
- When the AE stopped (stop date or an indication of "ongoing").
- Severity of the AE.
- Seriousness (e.g., hospitalization or death).

- Actions taken.
- Outcome.
- Investigator opinion regarding the AE relationship to the study drug(s).

10.2.4. Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may continue in the study at the discretion of Axsome after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, or for which continued administration of the study drug is not reasonable in view of the potential benefit to the subject, the investigator must decide whether to stop the study and/or treat the subject. Special procedures may be recommended for the specific study drug, such as the collection of a serum sample for blood concentrations of the study drug, specific tapering procedures, or treatment regimens, as appropriate.

10.2.5. Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after the subject's last visit in the study) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate eCRF.

10.2.6. Notification of Serious Adverse Events

The investigator or designee must report all SAEs within 24 hours of first becoming aware of the event by completing the Serious Adverse Event Report Form. [redacted] At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number.
- Reporter (study site and investigator).
- Subject's study number.
- Subject's year of birth.
- Subject's sex.
- Date of last dose of study drug.
- Adverse event term.
- Date of occurrence of the event.
- A brief description of the event, outcome to date, and any actions taken.
- The seriousness criteria(on) that were met.
- Concomitant medication at onset of the event.
- Relevant past history information.
- Relevant laboratory test findings.
- Investigator's opinion of the relationship to the study drug(s). ("Is there a reasonable possibility that the study drug caused the SAE? Yes, or No?").

The investigator must also promptly provide any available supporting information which is requested after review of the initial SAE Report Form.

Any missing or additional relevant information concerning the SAE should be provided in a follow-up SAE Report Form. Ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidance's) regarding the notification of his or her health authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), principal and coordinating investigators, study investigators, and institutions. The detailed reporting duties and division of responsibilities between Axsome and designated vendors will be provided in a separate document. Each investigator is obligated to learn about the reporting requirements for investigators in his or her country. The study monitor may be able to assist with this.

10.2.6.2 Adverse Drug Reactions

Axsome will report all ADRs related to the study drug to the proper health authorities; serious ADRs will be reported immediately and nonserious ADRs will be reported after completion of the study. Suspected serious adverse drug reactions must be reported to Axsome immediately, regardless of the time that has elapsed since the end of the period of observation.

10.2.6.3 Nonserious Adverse Events

Axsome will review nonserious AEs that are recorded in the eCRF on a regular basis.

10.3. Special Considerations

10.3.1. Adverse Events of Special Interest

No AEs of special interests have been defined for this study.

10.3.2. Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control (from Day 1 through 30 days beyond the End of Study) and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted before administration of the study drug on every female of childbearing potential. A woman who is found to be pregnant at Visit 1 will be excluded from the study and considered a screen failure.

A woman who becomes pregnant during study drug treatment will be immediately discontinued from study participation. The investigator must report the pregnancy in the same timeline as an SAE (within 24 hours of learning of the pregnancy). The investigator should record information related to the pregnancy on the Pregnancy and Lactation Exposure Form provided by Axsome or its designee. Pregnancy is not considered an AE.

Early termination visit assessments are required as soon as possible after learning of the pregnancy with documentation of pregnancy as the reason for early termination.The investigator is also responsible for following the pregnancy until termination or 1 month after live birth. Findings must be reported on the Pregnancy and Lactation Exposure Form or Query Response Form and reported to Axsomeor its designee. The event meets the SAE criterion only if it results in a spontaneous abortion or acongenital anomaly.

10.3.3. Overdose

Subjects should not be more than 120% compliant between study visits.

Overdose that occurs during the study will be treated and documented as an AE/UAE/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, subject identification, study drug, dose, action taken (e.g., administration of antidote [if available] or supportive measures or therapy), and any comments.

11. DATA SAFETY MONITORING BOARD

No Data Safety Monitoring Board will be convened during the study.

12. STATISTICS

This section describes the statistical methods to be used to analyze efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final CSR will discuss deviations from the SAP, if any.

12.1. Study Endpoints

12.1.1. Primary Endpoints

The primary safety variable is long-term safety as measured by the incidence of TEAEs following dosing with AXS-05.

12.1.2. Secondary Endpoints

The secondary endpoints for this study are:

Safety Measures:

- Change in vital signs (blood pressure and heart rate) over time
- Change in ECG findings over time
- Change in clinical laboratory measures over time
- Incidence of suicidal behavior, as identified via the C-SSRS

Efficacy Measures:

- Change in MADRS
- CGI-I
- CGI-S
- Change in HAM-A over time
- Change in CPFQ over time
- Change in Q-LES-Q over time
- Change in SDS over time

12.2. Sample Size Determination

This study will enroll approximately 150 subjects. This sample size will allow for an assessment of the long-term safety and efficacy in patients with TRD.

12.3. Analysis Populations

The following analysis populations are planned for this study:

- Safety Population: The Safety Population will include all subjects who take at least one dose of study drug.

Descriptive statistics will be used for all variables and all data over time.

12.4. Statistical Analyses

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a *P* value of less than or equal to 0.05 will be considered statistically significant. Furthermore, the baseline will be the last assessment before the first dosing of the study drug.

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

12.4.1. Study Subjects and Demographics

12.4.1.1. Disposition and Withdrawals

The numbers of subjects completing, withdrawing, and discontinuing treatment, along with reasons for discontinuation or withdrawal, will be tabulated.

12.4.1.2. Protocol Deviations

Major protocol deviations will be classified and documented by Axsome before database lock and will be discussed in the CSR. All protocol deviations, both minor and major,will be presented in a data listing.

12.4.1.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, weight, and height) will be summarized by descriptive statistics. Medical history will be listed.

Prior and concomitant medications will be summarized by the number and percentage of subjects taking each medication, classified using World Health Organization (WHO) Drug Dictionary, Anatomical Therapeutic Chemical (ATC) classes, and preferred terms.

12.4.2. Exposure and Compliance

Study drug administration will be summarized in terms of exposure and doses taken.

12.4.3. Safety and Efficacy Analyses

Variables will be summarized and analyzed using the Safety Population unless otherwise specified. Full details of the analysis will be outlined in the SAP.

12.4.4. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) reporting system.

The number and percentage of subjects with TEAEs will be displayed by SOC and preferred term. Additionally, TEAEs will be tabulated by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable.

12.4.5. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oral body temperature, and weight.

12.4.6. Clinical Laboratory Values

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for each laboratory value.

12.4.7. Electrocardiogram Values

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for each ECG parameter.

12.4.8. Physical Examination Findings

Physical examination data will be presented in the listings.

13. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

13.1. Sponsor and Investigator Responsibilities

13.1.1. Sponsor Responsibilities

Axsome is obligated to conduct the study in accordance with strict ethical principles (Section 15). Axsome reserves the right to withdraw a subject from the study (Section 7.3), to terminate participation of a study site at any time (Section 13.5.3), and/or to discontinue the study (Section 13.5.2).

Axsome agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

13.1.2. Investigator Responsibilities

By signing the Investigator's Agreement (Section 17), the investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to conduct the studyin accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities (Section 15.1 and Appendix B). While delegation of certain aspects of the study to sub investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing Axsome with documentation of the qualifications, Good Clinical Practice (GCP) training, and research experience for themselves and their staff as required by Axsome and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

13.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from Axsome that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

- The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
- All regulatory/GCP documents have been submitted to and approved by Axsome.
- The study site has a Clinical Trial Agreement in place.
- Study site personnel, including the investigator, have participated in a study initiation meeting/visit.

13.3. Study Documents

All documentation and material provided by Axsome for this study are to be retained in a secure location and treated as confidential material.

13.3.1. Investigator's Regulatory Documents

The regulatory documents are listed as follows:

- Signed original protocol (i.e., Investigator's Agreement).
- Curricula vitae of the principal investigator and sub investigators.
- Name and address of the laboratories.
- List of laboratory reference ranges, and if available, a quality certificate.
- Form Signature Log/Delegation of Study-related Duties.
- Any other relevant GCP documents.

The regulatory documents must be received from the investigator and reviewed and approved by Axsome before the study site can initiate the study and before Axsome will authorize shipment of study drug to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the AXS-05 Investigator's Brochure, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and study drug accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

13.3.2. Case Report Forms

By signing the Investigator's Agreement (Section 17), the investigator agrees to maintainaccurate eCRFs and source documentation as part of the case histories for all subjects who sign anICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. Axsome or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by Axsome or its designee.

The eCRFs may be signed by the investigator or a sub investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

13.3.3. Source Documents

All information recorded in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Before the study starts, a list identifying any data to be recorded directly on the eCRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to Axsome as well as the investigator. A copy of the laboratory results should be retained with each subject's source data.

13.4. Data Quality Control

Axsome and its designees will perform quality control checks on this clinical study.

13.4.1. Monitoring Procedures

Axsome will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Axsome personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review the following:

- Source documents, directly comparing entries in the EDC system with the source documents.
- Investigator regulatory documents (Section 13.3.1).
- Consenting procedures.
- AE procedures.
- Storage and accountability of the study drug and study materials.

The CRA will ask for clarification and/or correction of any noted inconsistencies. As representatives of Axsome, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the CRAs in their activities, if requested. Further, the investigator agrees to allow Axsome or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

13.4.2. Data Management

Axsome or its designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP

and Axsome or its vendors' standard operating procedures (SOPs). A comprehensive data management plan will be developed including a data management overview, database contents, annotated CRF, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the CRF completion guidelines.

13.4.3. Quality Assurance/Audit

This study will be subject to audit by Axsome or its designee in accordance with Axsome's SOPs in order to evaluate compliance with the protocol, SOPs, GCP, and regulatory requirements.

Axsome or its designee may conduct audits on a selection of study sites, requiring accessto subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Axsome immediately.

13.5. Study Termination

The study may be terminated at Axsome's discretion at any time and for any reason.

13.5.1. Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Axsome will notify the IRBs/IECs and regulatory authorities on the regular termination of the study as required according to national laws and regulations.

13.5.2. Premature Study Termination

The study may be terminated prematurely for any reason and at any time by Axsome, IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Axsome or its designee will notify the IRB/IEC and regulatory authorities as appropriate on the premature termination as required according to national laws and regulations. Axsome or its designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators must inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination Visit.

13.5.3. Study Site Closure

A study site's participation in the study may be terminated at any time by Axsome. At the end of the study, all study sites will be closed. This will include the investigator's final approval and lock

of all patient data, return of unused study material and investigational product unless otherwise provided for in writing by Axsome, and final visits by study monitors.

13.5.4. Record Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be separated into two categories: investigator's study file and patient clinical source documents.

The investigator's study file will contain the protocol and protocol amendments (if applicable), eCRF guidelines, IRB / IEC approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence.

Patient clinical source documents (which are usually defined by the project in advance to record key efficacy and/or safety parameters independent of the eCRF) may include patient and/or hospital clinical records, physician's and nurse's notes, appointment book, original laboratory reports, X-ray, pathology and special assessment reports, consultant's letters, screening and enrollment log, etc.

The patient's involvement in the study should be clearly documented in the study site's clinical records. Details should include the study protocol number, the patient's enrollment number, the patient's consent to take part in the study (including the date of consent), the dates of all study visits, details of any treatments withdrawn because of study participation, the dates of dispensing study drug, details of any AEs (including any SAEs), and changes in concomitant medications.

Study documents should not be destroyed without prior written agreement between Axsome and the investigator. If the investigator wishes to assign the study records to another party or move them to another location, Axsome must be notified in advance.

If the investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the investigator and Axsome to store these in a sealed container(s) outside the site. The sealed container(s) can therefore be returned to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside the site.

13.6. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Axsome. The protocol amendment must be signed by the investigator and approved by the IRB/IEC before it may be implemented at a site. Protocol amendments will be filed with the appropriate regulatory agencies having jurisdiction over the conduct of the study.

13.7. Use of Information and Publication

All information concerning AXS-05, Axsome's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Axsome or its designee to the investigator and not previously published, is considered confidential and remains the sole property of Axsome. CRFs also remain the property of Axsome. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of Axsome.

The information developed in this study will be used by Axsome in connection with the continued development of AXS-05 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Axsome. Publication or other public presentation of AXS-05 data resulting from this study requires prior review and written approval of Axsome. Abstracts, manuscripts, and presentation materials should be provided to Axsome for review and approval at least 30 days before the relevant submission deadline. Data from individual study sites must not be published separately, unless otherwise agreed to in writing by the Axsome.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Axsome has reviewed and commented on such a presentation or manuscript for publication.

14. FINAL CLINICAL STUDY REPORT

Axsome will retain ownership of the data generated from the study.

The final CSR will be written after completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 1996 Version of the Declaration of Helsinki, and the applicable regulations of the countries in which the study is conducted.

See Appendix B for regulations and guidelines.

15.2. Subject Information and Informed Consent

A properly constituted, valid IRB/IEC must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent before enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (i.e., objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the

investigator for possible inspection by regulatory authorities, Axsome, and/or designated personnel. Collection of informed consent must be documented on the eCRF.

Furthermore, the subject will be informed that if he or she wishes to dropout or withdraw (see Section 7.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

15.3. Approval by Institutional Review Board and Independent Ethics Committee

For investigational new drug studies, the minimum standards of conduct and requirements for informed consent are defined in the US FDA regulations.

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the Axsome monitor before shipment of investigational drug supplies and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed Axsome IRB Approval Form or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Axsome must receive their written approval before implementation. This written approval will consist of a completed IRB/IEC approval form or written documentation from the IRB/IEC containing the same information.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and Axsome.

16. REFERENCES

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2. Guy, W., *ECDEU Assessment Manual for Psychopharmacology*. 1976, Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.

3. Endicott, J., et al., *Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure.* Psychopharmacol Bull, 1993. **29**(2): p. 321-6.

4. Sheehan, D.V., K. Harnett-Sheehan, and B.A. Raj, *The measurement of disability.* Int Clin Psychopharmacol, 1996. **11 Suppl 3**: p. 89-95.

5. Hamilton, M., *The assessment of anxiety states by rating.* Br J Med Psychol, 1959. **32**(1): p. 50-5.

6. Fava, M., et al., *A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment.* J Clin Psychiatry, 2006. **67**(11): p. 1754-9.

7. Posner, K., et al., *The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* Am J Psychiatry, 2011. **168**(12): p. 1266-77.

17. INVESTIGATOR'S AGREEMENT

PROTOCOL NUMBER:	AXS-05-TRD-202
PROTOCOL TITLE:	An Open-Label Study to Assess the Long-term Safety and Efficacy of AXS-05 in Subjects with Treatment Resistant Depression.
PROTOCOL VERSION:	Amendment 2: November 8, 2021

I have read this protocol and the investigator's brochure and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Axsome and its designated vendors during the study. I carry out the study in accordance with the revised Declaration of Helsinki 1996. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on a study drug during and after study completion.

Having considered fully all the available information, I consider it is ethically justifiable to give the study drug to selected subjects in my care according to the study protocol. I:

- Agree to use the study material, including the study drug, only as specified in the protocol and understands that changes cannot be made to the protocol without prior written approval from Axsome.
- Understand that any violation of the protocol may lead to early termination of the study.
- Agree to report to Axsome within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to administration of the study drug.
- Agree to comply with Axsome and regulatory requirements for the monitoring and auditing of this study.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

APPENDICES

A. Address List

1. Sponsor

Name: Axsome Therapeutics, Inc.

[redacted]

[redacted]

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf