Document Type: Protocol

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

ClinicalTrials.gov Identifier: NCT03595579

Document Date: June 28, 2018

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- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information.
- Other information as needed to protect the confidentiality of Axsome Therapeutics, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

COMPOUND NAME/NUMBER:	AXS-05
PROTOCOL NUMBER:	AXS-05-MDD-201
[redacted]	[redacted]
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects with Major Depressive Disorder
PROTOCOL VERSION:	Final (v2.0)
PROTOCOL DATE:	28Jun2018

AXSOME
THERAPEUTICS

[redacted]

APPROVAL SIGNATURES

PROTOCOL NUMBER: AXS-05-MDD-201

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

PROTOCOL VERSION: Final (v2.0)

PROTOCOL DATE: 28Jun2018

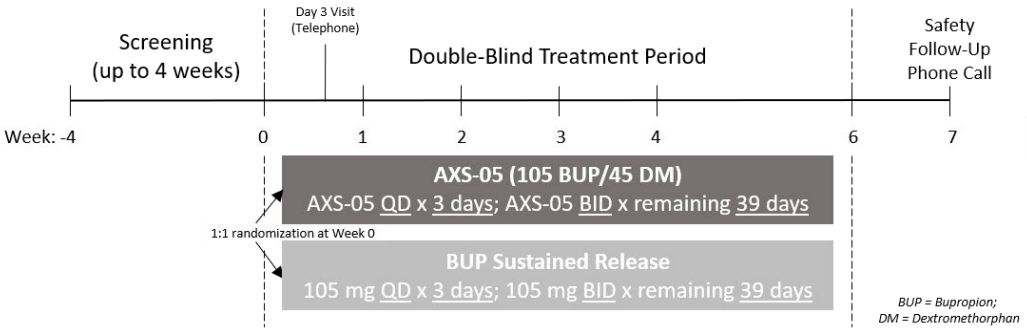
I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Study Contact and Details

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

1. SYNOPSIS

CLINICAL STUDY SYNOPSIS: AXS-05-MDD-201	
Product Name/ Number	AXS-05 (bupropion hydrochloride and dextromethorphan hydrobromide monohydrate)
Protocol Number	AXS-05-MDD-201
Protocol Title	A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects with Major Depressive Disorder
Indication	Treatment of Major Depressive Disorder (MDD)
Development Phase	2
Objective	To evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD
Study Design	This study is a randomized, double-blind, active-controlled, Phase 2 trial, consisting of a screening period of up to 4 weeks, and a 6-week treatment period. **Screening Period** Prior to randomization, all subjects will enter an up to four-week screening period (Screening) to determine eligibility. Eligible subjects must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features, based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version (SCID-5-CT), with a current major depressive episode of at least 4 weeks in duration. Eligible subjects must meet all other inclusion and no exclusion criteria. **Treatment Period** Randomization Subjects who successfully complete Screening will be randomly assigned at the baseline visit (Baseline) to receive either AXS-05 or bupropion sustained release (SR) in a 1:1 ratio for 6 weeks. The randomization schedule will be computer-generated using a permuted block algorithm that will randomly allocate the study drug to randomization numbers. Treatments Doses will be titrated as follows: • Days 1 - 3 o AXS-05 group: 105 mg bupropion, 45 mg dextromethorphan QD o Bupropion group: 105 mg bupropion QD • Days 4 - 42 o AXS-05 group: 105 mg bupropion, 45 mg dextromethorphan BID o Bupropion group: 105 mg bupropion BID All QD doses will be taken in the morning, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All BID doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All study drug is of identical appearance and similar weight in order to maintain the integrity of the blind. **Assessments and Visits** Study visits will occur at Screening (Visit 1), Baseline (Day 0, Visit 2), and on Days 3, 7, 14, 21, 28, 42 and 49 (Visits 3 – 9). Study procedures and assessments will be performed during study visits as outlined in the Schedule of Assessments. Visit 3 (Day 3) will be conducted telephonically. Subjects will be reminded during Visit 3 to begin BID dosing on Day 4. All subjects completing 6 weeks of treatment or subjects prematurely discontinuing from the study will be required to complete a follow-up visit one week after the last dose of study drug, Visit 9, telephonically.

	Assessments will include safety parameters, MADRS, QIDS-SR-16, CGI-S and CGI-I. [redacted] Study drug compliance will also be assessed at the 80% level by counting the number of tablets dispensed and returned. Noncompliant subjects are subject to early termination from the study. **AXS-05-MDD-201 Study Design** 
Planned Number of Subjects	A sufficient number of subjects will be screened to achieve the goal of having approximately 60 compliant subjects complete the 6-week treatment period.
Study Centers	Up to approximately 5 U.S. study centers
Diagnosis and Subject Selection Criteria **-Inclusion Criteria** **-Exclusion Criteria**	**Inclusion Criteria**: 1. 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. 2. Male or female outpatients, 18 to 65 years of age, inclusive. 3. Currently meets the DSM-5 criteria for MDD without psychotic features, based on the SCID-5-CT, with a current major depressive episode of at least 4 weeks in duration at Visit 1. 4. MADRS score of ≥ 25 and CGI-S ≥ 4 at Screening (Visit 1) and Baseline (Visit 2). 5. Normal physical examination findings and clinical laboratory test results from Screening (Visit 1) or abnormal results that are judged not clinically significant by the investigator. 6. Body mass index (BMI) between 18 and 40 kg/m^2, inclusive. 7. If female of childbearing potential, having a negative urine pregnancy test result at Visit 1 and Visit 2, and practicing an adequate method of birth control (e.g. oral or parenteral contraceptives, intrauterine device, double-barrier) and does not plan to become pregnant during the course of the study. Long-term abstinence is acceptable as long as the subject agrees to use double-barrier contraception if they decide to have sexual intercourse. 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. Female subjects may be included without a negative urine pregnancy test if they are surgically sterile or at least 2 years post-menopausal. Male subjects and their female sexual partners should use an acceptable method of birth control (as noted above) during the study. **Exclusion Criteria:** ***Psychiatric Criteria:*** 1. History of:

	a. Any depressive episode with psychotic or catatonic features b. Any manic, hypomanic or mixed episode, including bipolar disorder (Type 1 or Type 2) and substance-induced (e.g. antidepressant-induced) manic, hypomanic/mixed episode c. Schizophrenia, schizoaffective, or other psychotic disorder d. Panic disorder, with or without agoraphobia e. Obsessive-compulsive disorder f. Bulimia or anorexia nervosa g. Any persistent neurocognitive disorder h. Any other anxiety disorder which has been the primary focus of clinical attention for the six months prior to Screening, while MDD was a secondary focus of attention 2. History of treatment resistant depression defined as 2 or more failed treatments of adequate dose and duration in the current depressive episode. 3. Post-traumatic stress disorder, active within 3 years of Visit 1. 4. Borderline or antisocial personality disorder or other disorder of sufficient severity to interfere with participation in this study. 5. Alcohol/substance use disorder (other than nicotine or caffeine), active within 1 year of Visit 1. 6. Psychiatric hospitalization within current depressive episode. 7. Psychiatric symptoms secondary to any other general medical condition. 8. Clinically significant risk of suicide or harm to self or others. Risk of suicide is determined by meeting any of the following criteria: a. In the judgment of the investigator, the subject may be a significant risk for suicide as judged by the psychiatric interview or information collected in the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1 or Visit 2 (e.g., The subject responded "yes" to question 4 or question 5 on the screening C-SSRS, and the most recent episode occurred within the current depressive episode). b. The subject has attempted suicide within the current depressive episode. c. MADRS Item 10 score ≥ 5 at Visit 1 or Visit 2. ***Treatment-Related Criteria:*** 9. Use of drugs that are strong inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, quinidine) as defined in FDA's Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. 10. Use of drugs that are inhibitors of CYP2B6, the primary enzyme that metabolizes bupropion (e.g. clopidogrel, ticlopidene, prasugrel), or that are inducers of CYP2B6 (e.g. ritonavir, lopinavir, efavirenz). Please refer to the Wellbutrin SR (bupropion) FDA package insert. 11. Current use, or use within 14 days before Visit 1 of monoamine oxidase inhibitors (MAOIs), or linezolid, or intravenous methylene blue. 12. Use of opioids (e.g., codeine, oxycodone, morphine) within 14 days before Visit 1. 13. Having received any prohibited medications, supplements or herbal products [redacted], including any antipsychotic, anticonvulsant/mood stabilizer, anxiolytic, benzodiazepine, ADT, or ADT augmentation agent (e.g., T3 [except as treatment for thyroid condition], 2nd antidepressant, etc.) within 1 week or 5 half- lives of the medication, whichever is longer, prior to Visit 2; however, 4 weeks is required for T3, 2 weeks is required for MAOIs. Lithium must be tapered and followed by a 1-week washout. The safe withdrawal from benzodiazepine treatment should be decided by the patient's treating clinician and also monitored by the principal investigator. 14. History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1 (whichever is longer). 15. Requiring concomitant treatment with any of the prohibited medications, supplements, or herbal products [redacted], including any psychotropic drug or any drug with

psychotropic activity or with a potentially psychotropic component, except for the following:
   a. Eszopiclone, zolpidem, zolpidem extended-release, zopiclone or zaleplon for insomnia may be continued provided the medication has been used in a consistent manner for 4 weeks prior to enrollment and at doses that do not exceed the maximum labeled amounts.
16. Initiation or termination of psychotherapy for depression within 3 months of Visit 1, or plans to initiate, terminate, or change such therapy during the course of the study (Support meetings or counseling [e.g., marital counseling] are allowed provided they are no more frequent than weekly and do not have treatment of depression as their objective).
17. Ongoing, initiation or termination of phototherapy within 1 month of Visit 1.

Other Medical Criteria:

18. 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).
19. Female subjects who meet either of the following criteria:
   a. Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study.
   b. Sexually active females who are less than 2 years postmenopausal, and are either not surgically sterile (tubal ligation, bilateral oophorectomy or hysterectomy), or not practicing a reliable method of contraception that will continue throughout the duration of the study. Reliable contraception is defined as oral contraceptives (consisting of an estrogen-progestin combination or progestin alone), transdermally delivered contraceptives (e.g., Ortho Evra), depot injections (e.g., Depo-Provera), vaginal contraceptive ring (e.g. NuvaRing), contraceptive implants (e.g., Implanon, Norplant II/Jadelle), an intrauterine device, or double-barrier method (e.g. diaphragm plus condom accepted). Females using a hormonal contraceptive or intrauterine device must have been doing so for at least 1 month before Visit 1 and must follow that product's package insert instructions including additional protection at times when hormonal contraceptive doses might be missed. Rhythm, withdrawal, single-barrier methods (i.e., contraceptive sponge, female condom or male condom or diaphragm alone) are not acceptable methods of contraception. Long-term abstinence is acceptable as long as patients agree to use double-barrier contraception if they decide to have sexual intercourse.
20. Positive serum ethanol test or urine drug screen (UDS) for any prohibited medication or drugs of abuse (cocaine, marijuana, PCP, opioid or other agent that in the opinion of the investigator is being abused) at Visit 1. Subjects should be advised not to drink alcohol for at least 8 hours prior to screening labs.
21. 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.
22. Hypertension defined as resting, sitting systolic blood pressure (BP) $\geq$150 mm Hg or diastolic blood pressure $\geq$ 95 mm Hg. Patients with high BP (as defined above) may be accepted in the study if they subsequently have acceptable BP values on reassessment at least 30 minutes apart.
23. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month before Visit 1 (Serum TSH must be $> 0.75 \times$ the LLN and $< 1.25 \times$ ULN).
24. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g. codeine, etc.), or any other ingredient in the study medication.

	25. History of intolerance to bupropion or dextromethorphan. 26. Patients who have received dextromethorphan co-administered with quinidine (e.g. Nuedexta®) within the past four weeks. 27. Gastric bypass or any condition that would be expected to affect drug absorption (lap band procedures are acceptable if there is no problem with absorption). 28. Narrow-angle glaucoma without a patent iridectomy. 29. Known human immunodeficiency virus (HIV) infection. 30. Clinically significant signs of active hepatitis B and/or C infection. 31. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase and/or alanine aminotransferase) results > 2.0 x ULN. 32. Any clinically significant abnormality on the screening laboratory tests, as assessed by the study investigator and/or the medical monitor. 33. Treatment with any investigational drug within 30 days of Visit 1. 34. Currently hospitalized or residing in an in-patient facility during the study. 35. 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.
Test Product, Dosage, and Mode of Administration	Treatment A: AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet, oral
Reference Therapies, Dosage, and Mode of Administration	Treatment B: Bupropion SR (105 mg) matching tablet, oral
Treatment Regimen	Days 1 - 3 • AXS-05 group: 105 mg bupropion, 45 mg dextromethorphan QD • Bupropion group: 105 mg bupropion QD Days 4 - 42 • AXS-05 group: 105 mg bupropion, 45 mg dextromethorphan BID • Bupropion group: 105 mg bupropion BID All QD doses will be taken in the morning, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water. All BID doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water.
Study Duration	Up to 11 weeks: up to 4 weeks screening, followed by 6 weeks of treatment, followed by a 1-week follow-up visit.
Criteria for Evaluation	**Safety assessments will include:** • Adverse Event (AE) recording • Adverse Dropouts (ADOs) • Incidence of Treatment Emergent Adverse Events (TEAEs) • Clinical laboratory test results • Vital sign measurements • Physical examinations • Columbia - Suicide Severity Rating Scale (C-SSRS)

Statistical Methods	**Analysis Populations:** The following analysis populations are planned for this study: ▪ *Modified Intent-to-Treat (mITT) Population*—the mITT will consist of all subjects who are randomized, subsequently take at least 1 dose of the study drug, and have at least 1 post-Baseline assessment ▪ *Intent-to-Treat Population*—the ITT will include all subjects who are randomized ▪ *Safety Population*—the Safety Population will be the primary safety analysis population and will include all subjects who receive at least 1 dose of the study drug All analyses, including safety analyses, will be detailed in the statistical analysis plan.
Sample Size Determination	Approximately 60 subjects (30 per arm), who are compliant and who complete the 6-week treatment period, are planned for this study. The sample was determined based on prior reported experience with trials of a similar stage, in a similar patient population, with a similar objective. A sufficient number of subjects will be screened to achieve the planned number of subjects.

Schedule of Assessments

Visit	Screening Visit 1	Baseline Visit 2	Phone Call Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 / ET	Visit 9 Follow-up[a]
Study Day	**-28 to -1**	**0**	**3 (+1)**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**42 (±2)**	**49 (±2)**
Week	**-4 to -1**			**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 7**
Informed Consent	X[b]								
Inclusion/Exclusion Criteria	X	X							
Demographics	X								
Medical/Psychiatric History	X								
Medication History	X								
Physical Examination	X							X	
Vital Signs, Height/Weight[c]	X	X		X	X	X	X	X	
Laboratory Tests[d]	X							X	
Urine Drug Screen[e]	X	X						X	
Serum Ethanol[e]	X							X	
Urine Pregnancy Test (all female subjects)	X	X						X	
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SCID-5-CT	X								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MADRS	X	X		X	X	X	X	X	
QIDS-SR-16	X	X		X	X	X	X	X	
CGI-S (Severity)	X	X		X	X	X	X	X	
CGI-I (Improvement)				X	X	X	X	X	
C-SSRS	X	X		X	X	X	X	X	X
Randomization		X							
Instruct to begin BID dosing			X						
Study Drug Dispensation[h]		X		X	X	X	X		
Study Drug Accountability			X	X	X	X	X	X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

Abbreviations: SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version; ET = early termination; EOS = End of Study; MADRS = Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self- Rated; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia - Suicide Severity Rating Scale; [redacted]

a Safety follow-up visit to be performed telephonically.
b Informed consent must be signed prior to any study procedures being performed.
c Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a seated position for at least 5 minutes. Height will be measured at Visit 1 and weight at Visit 1 and Visit 8 (EOS or ET).
d Clinical laboratory tests will include hematology, serum chemistry, urinalysis and thyroid panel.
e May be performed at other study visits per investigator judgment. Subjects with positive urine drug screen or serum ethanol levels at Visit 1 may be allowed in study depending on circumstances described to the Medical Monitor and a negative repeat UDS is obtained before Visit 2.
f [redacted]
h Subjects will begin to take study drug the morning of Day 1 (morning after Visit 2).

2. TABLE OF CONTENTS

LIST OF FIGURES

2.1 List of Figures

3. LIST OF ABBREVIATIONS

ADOs	Adverse Dropouts
ADR	Adverse Drug Reaction
ADT	Antidepressant Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AUC	Area Under the Curve
AXS	Axsome Therapeutics
BID	Twice Daily (bis in die)
BMI	Body Mass Index
BP	Blood Pressure
BUP	Bupropion
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement of Illness
CGI-S	Clinical Global Impression of Severity of Illness
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
C-SSRS	Columbia – Suicide Severity Rating Scale
DM	Dextromethorphan
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
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 Inhibitors
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-Treat Population
NJ	New Jersey
NMDA	N-methyl-D-aspartate
NY	New York
OTC	Over-the-Counter
PI	Principal Investigator
PK	Pharmacokinetic
QD	Once Daily (quoque die)
QIDS-SR-16	Quick Inventory of Depressive Symptomatology-Self- Rated
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SD	Standard Deviation
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
SOC	System Organ Class
SR	Sustained Release
SSRIs	Selective Serotonin Reuptake Inhibitors
TEAE	Treatment-Emergent Adverse Events
TMF	Trial Master File
TSH	Thyroid-Stimulating Hormone
U.S.	United States
UADR	Unexpected Adverse Drug Reaction
UAE	Unexpected Adverse Event
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
USA	United States of America
[redacted]	[redacted]

4. INTRODUCTION

4.1 Background

Major Depressive Disorder (MDD) is a debilitating psychiatric disorder characterized by depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period, and which impairs social, occupational, educational, or other important functioning. MDD is highly prevalent and difficult to treat. In 2016, 6.7 percent of adults aged 18 or older (16.2 million adults) had at least one Major Depressive Episode (MDE) in the past year, and 4.3 percent of adults (10.3 million adults) had an MDE with severe impairment in the past year. Adults in 2016 who had an MDE with severe impairment represented nearly two-thirds (64.0 percent) of adults who had a past year MDE. [1]. Results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicate that nearly two-thirds of treated patients with MDD do not experience adequate treatment response with first-line therapy, and that the majority of these initial failures also fail second-line treatment [2], suggesting that there are significant limitations to current treatments. There is therefore an urgent need for new, mechanistically novel treatments for MDD.

4.2 Rationale for the Evaluation of AXS-05 for Major Depressive Disorder

AXS-05 is being evaluated in the current study in subjects with MDD. AXS-05 is a fixed-dose combination of bupropion and dextromethorphan (DM). The bupropion in the combination is used both for its neuropharmacological properties as well as for its ability to inhibit the metabolism of DM through CYP2D6. The rationale for the study of AXS-05 in depressive disorders is based on the neuropharmacology of DM and bupropion which are relevant to depression, clinical observations with these individual agents in depressed subjects, and the positive pharmacokinetic interaction of DM and bupropion.

Bupropion and DM each target different receptor systems that are associated with antidepressant activity. Bupropion is an inhibitor of the neuronal uptake of norepinephrine and dopamine [3]. DM is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist and inhibitor of the serotonin transporter (SERT) and norepinephrine transporter (NET) [4]. Combining the distinct and independent mechanisms of action of these two compounds may be additive or synergistic.

The clinical utility of DM has however been limited by its rapid metabolism through CYP2D6 in the majority of humans yielding low plasma levels even at high and repeated doses [5]. AXS-05 addresses this limitation by combining DM and bupropion. 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 (Axsome data on file). Administration of bupropion in combination with DM 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 in the combination groups as compared to a group receiving bupropion alone. The positive pharmacokinetic interaction between bupropion and DM therefore enables DM's clinical utility in treating depression by increasing DM's plasma levels into a potentially therapeutic range.

[redacted]

5. OBJECTIVES

To evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD.

6. STUDY DESIGN

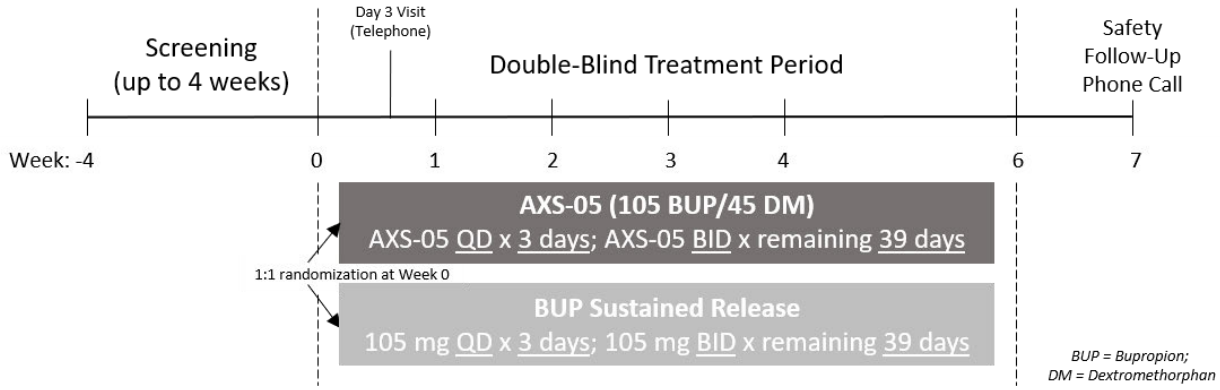
6.1 Overall Study Design and Plan

This study is a randomized, double-blind, active-controlled, Phase 2 trial, consisting of a screening period and a 6-week treatment period. The trial is being conducted in subjects experiencing a current depressive episode. Informed consent will be obtained before any subsequent screening related procedures are performed. Assessments will include safety parameters, MADRS, QIDS-SR-16, CGI-S and CGI-I. Subjects will be provided a Visual Analog Mood Scale (VAMS) and asked to complete it daily.

The study will be divided into 3 segments: an up to four-week screening period (Screening); a 6-week treatment period; and a 1-week follow-up period. A sufficient number of subjects will be screened and randomized to achieve the goal of having approximately 60 compliant subjects who complete the double-blind treatment period.

The study design is depicted in Figure 6.1.

Figure 6.1 Study Design



Screening Period

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

Treatment Period

Subjects who successfully complete Screening will be randomly assigned at Visit 2 (Baseline) to receive either AXS-05 or bupropion sustained release (SR) in a 1:1 ratio for 6 weeks. The treatments will be up-titrated in the following manner:

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

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

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

All study drug including AXS-05 tablets and bupropion SR tablets are of identical appearance and similar weight in order to maintain the integrity of the blind.

Assessments and Visits

Study visits will occur at Visit 1, Baseline (Day 0, Visit 2), and on Days 3, 7, 14, 21, 28, 42 and 49 (Visits 3 – 9). Study procedures and assessments will be performed during study visits as outlined in the Schedule of Assessments (See Section 17.2). Visit 3 (Day 3) will be conducted telephonically. Subjects will be reminded during Visit 3 to begin BID dosing on Day 4. All subjects completing 6 weeks of treatment or subjects prematurely discontinuing from the study will be required to complete a follow-up visit one week after the last dose of study drug (Visit 9), telephonically.

Assessments will include safety parameters, MADRS, QIDS-SR-16, CGI-S and CGI-I. [redacted]

[redacted]

[redacted]

[redacted]Study drug compliance will also be assessed at the 80% level by counting the number of tablets dispensed and returned. Non-compliant subjects are subject to early termination from the study and should return for an Early Termination visit.

Safety will be assessed by evaluating treatment-emergent AEs (TEAEs); clinical laboratory test results; vital sign measurements; and physical examination findings.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent form [ICF] through follow up) will be documented.

6.2 Discussion of Study Design

The safety assessments used in this study are recognized and validated standards of measurement.

Bupropion SR is used as an active control in this trial as it is one of the two components in AXS-05. The 3-day up-titration period for AXS-05 and bupropion SR used in this trial is meant to minimize AEs resulting in early drop-outs. This up-titration from QD to BID dosing is consistent with the label for Wellbutrin SR which recommends at least 3 days before up-titrating to BID dosing. No down-titration has been included consistent with the product label for Wellbutrin SR.

6.3 Study Sites

The study will take place at up to 5 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 information provided to the subject and in the ICF.

7. SUBJECT POPULATION

7.1 Selection of Study Population and Diagnosis

Eligible subjects for this study must have a diagnosis of Major Depressive Disorder (MDD). A sufficient number of subjects will be screened to achieve the goal of having approximately 60 compliant subjects who complete the double-blind treatment period at up to 5 study centers in the U.S.

The diagnosis of MDD will be confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version SCID-5-CT.

Eligible subjects must have a current depressive episode of at least 4 weeks.

Eligible subjects are to have otherwise acceptable and stable general health as required by the inclusion and exclusion criteria, documented by medical history, physical examination, and clinical laboratory examinations.

7.2 Study Entry Criteria

7.2.1 Inclusion Criteria

A subject will be eligible for study participation if the subject meets all of the following criteria:

1. 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.
2. Male or female outpatients, 18 to 65 years of age, inclusive.
3. Currently meets the DSM-5 criteria for MDD without psychotic features, based on the SCID-

5-CT, with a current major depressive episode of at leave 4 weeks in duration at Visit 1.

4. MADRS score of ≥ 25 and CGI-S ≥ 4 at Screening (Visit 1) and Baseline (Visit 2).
5. Normal physical examination findings and clinical laboratory test results from Screening (Visit 1) or abnormal results that are judged not clinically significant by the investigator.
6. Body mass index (BMI) between 18 and 40 kg/m^2, inclusive.
7. If female of childbearing potential, having a negative urine pregnancy test result at Visit 1 and Visit 2, and practicing an adequate method of birth control (e.g. oral or parenteral contraceptives, intrauterine device, double-barrier) and does not plan to become pregnant during the course of the study. Long-term abstinence is acceptable as long as the subject agrees to use double-barrier contraception if they decide to have sexual intercourse. 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. Female subjects may be included without a negative urine pregnancy test if they are surgically sterile or at least 2 years post-menopausal. Male subjects and their female sexual partners should use an acceptable method of birth control (as noted above) during the study.

7.2.2 Exclusion Criteria

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

Psychiatric Criteria:

1. History of:
   a) Any depressive episode with psychotic or catatonic features
   b) Any manic, hypomanic or mixed episode, including bipolar disorder (Type 1 or Type 2) and substance-induced (e.g. antidepressant-induced) manic, hypomanic/mixed episode
   c) Schizophrenia, schizoaffective, or other psychotic disorder
   d) Panic disorder, with or without agoraphobia
   e) Obsessive-compulsive disorder
   f) Bulimia or anorexia nervosa
   g) Any persistent neurocognitive disorder
   h) Any other anxiety disorder which has been the primary focus of clinical attention for the six months prior to Screening, while MDD was a secondary focus of attention
2. History of treatment resistant depression defined as 2 or more failed prior treatments of adequate dose and duration in the current depressive episode.
3. Post-traumatic stress disorder, active within 3 years of Visit 1.
4. Borderline or antisocial personality disorder or other disorder of sufficient severity to interfere with participation in this study.
5. Alcohol/substance use disorder (other than nicotine or caffeine), active within 1 year of Visit 1.
6. Psychiatric hospitalization within current depressive episode.
7. Psychiatric symptoms secondary to any other general medical condition.
8. Clinically significant risk of suicide or harm to self or others. Risk of suicide is determined by meeting any of the following criteria:

a) In the judgment of the investigator, the subject may be a significant risk for suicide as judged by the psychiatric interview or information collected in the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1 or Visit 2 (e.g., The subject responded "yes" to question 4 or question 5 on the screening C-SSRS, and the most recent episode occurred within the current depressive episode).
b) The subject has attempted suicide within the current depressive episode.
c) MADRS Item 10 score ≥ 5 at Visit 1 or Visit 2.

Treatment-Related Criteria:

9. Use of drugs that are strong inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine, quinidine) as defined in FDA's Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.
10. Use of drugs that are inhibitors of CYP2B6, the primary enzyme that metabolizes bupropion (e.g. clopidogrel, ticlopidene, prasugrel), or that are inducers of CYP2B6 (e.g. ritonavir, lopinavir, efavirenz). Please refer to the Wellbutrin SR (bupropion) FDA package insert.
11. Current use, or use within 14 days before Visit 1 of monoamine oxidase inhibitors (MAOIs), or linezolid, or intravenous methylene blue.
12. Use of opioids (e.g., codeine, oxycodone, morphine) within 14 days before Visit 1.
13. Having received any prohibited medications, supplements or herbal products [redacted], including any antipsychotic, anticonvulsant/mood stabilizer, anxiolytic, benzodiazepine, ADT, or ADT augmentation agent (e.g., T3 [except as treatment for thyroid condition], 2nd antidepressant, etc.) within 1 week or 5 half- lives of the medication, whichever is longer, prior to Visit 2; however, 4 weeks is required for T3, 2 weeks is required for MAOIs. Lithium must be tapered and followed by a 1-week washout. The safe withdrawal from benzodiazepine treatment should be decided by the patient's treating clinician and also monitored by the principal investigator.
14. History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1 (whichever is longer).
15. Requiring concomitant treatment with any of the prohibited medications, supplements, or herbal products [redacted] including any psychotropic drug or any drug with psychotropic activity or with a potentially psychotropic component, except for the following:
    a) Eszopiclone, zolpidem, zolpidem extended-release, zopiclone or zaleplon for insomnia may be continued provided the medication has been used in a consistent manner for 4 weeks prior to enrollment and at doses that do not exceed the maximum labeled amounts.
16. Initiation or termination of psychotherapy for depression within 3 months of Visit 1, or plans to initiate, terminate, or change such therapy during the course of the study (Support meetings or counseling [e.g., marital counseling] are allowed provided they are no more frequent than weekly and do not have treatment of depression as their objective).
17. Ongoing, initiation or termination of phototherapy within 1 month of Visit 1.

Other Medical Criteria:

18. 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).

19. Female subjects who meet either of the following criteria:
    a. Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study.
    b. Sexually active females who are less than 2 years postmenopausal, and are either not surgically sterile (tubal ligation, bilateral oophorectomy or hysterectomy), or not practicing a reliable method of contraception that will continue throughout the duration of the study. Reliable contraception is defined as oral contraceptives (consisting of an estrogen-progestin combination or progestin alone), transdermally delivered contraceptives (e.g., Ortho Evra), depot injections (e.g., Depo-Provera), vaginal contraceptive ring (e.g. NuvaRing), contraceptive implants (e.g., Implanon, Norplant II/Jadelle), an intrauterine device, or double-barrier method (e.g. diaphragm plus condom accepted). Females using a hormonal contraceptive or intrauterine device must have been doing so for at least 1 month before Visit 1 and must follow that product's package insert instructions including additional protection at times when hormonal contraceptive doses might be missed. Rhythm, withdrawal, single-barrier methods (i.e., contraceptive sponge, female condom or male condom or diaphragm alone) are not acceptable methods of contraception. Long-term abstinence is acceptable as long as patients agree to use double-barrier contraception if they decide to have sexual intercourse.
20. Positive serum ethanol test or urine drug screen (UDS) for any prohibited medication or drugs of abuse (cocaine, marijuana, PCP, opioid or other agent that in the opinion of the investigator is being abused) at Visit 1. Subjects should be advised not to drink alcohol for at least 8 hours prior to screening labs.
21. 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.
22. Hypertension defined as resting, sitting systolic blood pressure (BP) ≥150 mm Hg or diastolic blood pressure ≥ 95 mm Hg. Patients with high BP (as defined above) may be accepted in the study if they subsequently have acceptable BP values on reassessment at least 30 minutes apart.
23. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month before Visit 1 (Serum TSH must be > 0.75 × the LLN and < 1.25 × ULN).
24. History of allergy or hypersensitivity to bupropion, dextromethorphan, opiate drugs (e.g. codeine, etc.), or any other ingredient in the study drug.
25. History of intolerance to bupropion or dextromethorphan.
26. Patients who have received dextromethorphan co-administered with quinidine (e.g. Nuedexta®) within the past four weeks.
27. Gastric bypass or any condition that would be expected to affect drug absorption (lap band

procedures are acceptable if there is no problem with absorption).

28. Narrow-angle glaucoma without a patent iridectomy.
29. Known human immunodeficiency virus (HIV) infection.
30. Clinically significant signs of active hepatitis B and/or C infection.
31. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase and/or alanine aminotransferase) results > 2.0 x ULN.
32. Any clinically significant abnormality on the screening laboratory tests, as assessed by the study investigator and/or the medical monitor.
33. Treatment with any investigational drug within 30 days of Visit 1.
34. Currently hospitalized or residing in an in-patient facility during the study.
35. 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.

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 immediately if they withdraw consent to participate.

Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude 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 any reason. Examples of reasons for discontinuation may include: 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 case report form (CRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time a subject withdraws from the study.

Subjects who discontinue treatment should be encouraged to continue completing study visits and procedures so long as the subject does not withdraw consent.

7.4 Subject Replacement Criteria

Subjects who are withdrawn for noncompliance or other reasons may be replaced to achieve the goal of approximately 60 compliant subjects who complete the double-blind treatment period.

8. TREATMENTS

8.1 Identification of Investigational Product

The following study drugs will be provided:

Treatment A: AXS-05 (105 mg bupropion, 45 mg dextromethorphan) tablet, oral
Treatment B: Bupropion SR (105 mg) matching tablet, oral

AXS-05 is a fixed-dose combination tablet of 105 mg bupropion hydrochloride SR and 45 mg dextromethorphan hydrobromide monohydrate IR, in the form of a bilayer, film-coated tablet.

Bupropion SR tablets contain 105 mg bupropion hydrochloride SR, in the form of a film-coated tablet that matches the visual appearance and weight of the AXS-05 tablets.

AXS-05 and bupropion SR supplied for this study are manufactured by [redacted].

8.2 Labeling and Packaging

8.2.1 Labeling

Clinical labeling of the study drug will be performed by [redacted]. The bottles of 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, manufacture or expiration date, and Sponsor/manufacturer identification and dosing instructions.

8.2.2 Packaging

AXS-05 and bupropion SR tablets will be supplied and bottled by [redacted] and labeled at [redacted]. The study drug will be packaged in 50 cc bottles and labeled to blind the Investigator, the study clinic personnel, and subjects.

8.3 Study Drug Administration

All subjects will receive either AXS-05 or bupropion SR according to the kit number assigned by a randomization scheme. Eligible subjects will be assigned a unique kit that contains 4 bottles of study drug. Bottles from the assigned kits should be dispensed to the subject per the pharmacy manual and/or subject dosing instructions provided. The kit must remain on-site at all times and only the appropriate number of bottles should be dispensed to the subject at each study visit.

Designated staff at each site will dispense study drug bottles. Subjects will be instructed to take the study drug per the Treatment Period part of Section 6.1. Subjects should be instructed to return bottle(s) and any unused study drug at each study visit in order to record compliance. All study drug will be supplied and administered in a double-blind manner throughout the entire duration of the study.

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 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 study drug with a signature. A copy of this receipt must be kept by the Investigator and another copy will be stored at Axsome and/or its designee.

All study drug must be stored in an appropriate secure area (e.g., a locked cabinet in a locked room) at controlled room temperature (with a permitted range of 15°C-30°C or 59°F-86°F) and must be protected from heat and moisture. Any excursions below or above this temperature range should be communicated to Axsome Therapeutics, Inc., or its designee as soon as possible. The key to the storage area is to be kept by the Investigator or designee responsible for the study drug. The storage area will be accessible only to those persons authorized by the Investigator.

The key to the storage area is to be kept by the Investigator or designee responsible for the study drug. The storage area will be accessible only to those persons authorized by the Investigator.

8.5 Method of Assigning Subjects to Treatment Groups

Subjects who meet study entry criteria will be randomly assigned in a 1:1 ratio to AXS-05 or bupropion SR, respectively. The randomization schedule will be computer generated using a permuted block algorithm that will randomly allocate study drug to randomization numbers. The randomization numbers will be assigned sequentially. Study center will not be a blocking factor in the randomization schedule.

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

8.6 Blinding and Unblinding Treatment Assignment

All subjects, Investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified independent unblinded statistician, and clinical supply manager who will have access to the randomization code. The unblinded study personnel will not otherwise participate in study procedures or data analysis before unblinding of the study data to all study related personnel. Sponsor personnel involved in the management and monitoring of the study will be blinded to the treatment assignment.

Study personnel will strive to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, the site will access the randomization code. If the Investigator is not able to discuss treatment unblinding in advance, then he or she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. To unblind the treatment group, the Investigator will open the envelope in which the randomization code was received. The Investigator or designee must record the date and reason for study drug discontinuation on the appropriate CRF for that subject. In all nonemergency cases, the Investigator must discuss the event with the medical monitor before unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding those of the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he or she may or may not be asked to withdraw from the study. The Investigator will make this decision after consultation with the medical monitor.

8.7 Selection of Doses in the Study

The dose of AXS-05 (105 mg bupropion, 45 mg DM), titrated to twice daily, was selected based on the results of three completed Axsome-sponsored, pharmacokinetic Phase 1 trials of the combination of bupropion and DM. The selected dose combination resulted in an increase in DM plasma concentrations into a potentially therapeutic range.

The dose of bupropion SR is 105 mg, titrated to twice-daily administration. This dose was selected because it is equal to the dose of bupropion in AXS-05.

8.8 Selection of Timing of Dose

A significant food effect has not been reported for the individual components of AXS-05. AXS-05 and bupropion SR tablets are dosed on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) in this trial to match the dosing in the completed Phase 1 trials of AXS-05.

8.9 Dose Adjustment Criteria

Dose adjustment is not recommended in this study. If a subject misses a dose, or if a dose is skipped due to AEs, if possible the subject should continue in the study and take study drug at the designated times.

8.10 Drug Accountability

The Investigator 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 and initials) who received it. An inventory of study drug should be performed by authorized personnel upon receipt to confirm contents match the packing slip and that the all product packaging is received and in good condition. If product received does not correspond to the packing slip or is damaged, the Axsome study team should be contacted immediately and the inventory quarantined until further instructions are provided.

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 and appropriate regulatory agencies, as required.

Upon completion of the study, the study drug (partly used, unused, and empty packaging) 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 [redacted].

Subjects will be instructed to bring any unused study drug and empty containers to the clinic on Days 7, 14, 21, 28 and 42 (Visits 4 – 8), 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% level.

[redacted]

If non-compliance is determined, the site will be notified in writing and noncompliant subjects may be discontinued from the study. Discontinued subjects should return for an Early Termination visit, performing all the study assessments for Visit 8/ET and then complete the follow-up visit one week after the final dose of study drug (Visit 9).

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 at Screening (Visit 1) in the CRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the 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.

8.12.1 Prohibited Therapies

[redacted] The investigator should consult with the Axsome Medical Monitor if he/she is unsure whether a certain medication is prohibited.

Psychotherapy for depression may not be initiated, terminated, or changed during the course of the study (Support meetings or counseling [e.g., marital counseling] are allowed provided they are no more frequent than weekly and do not have treatment of depression as their objective).

Phototherapy is prohibited during the course of the study and may not have been initiated or terminated within 1 month of Visit 1.

Subjects who receive excluded therapies will be ineligible for continuation in the study at the discretion of the Sponsor and medical monitor.

8.13 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 (Section 17.2). 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 as soon as possible.

9.1 Study Periods, Visits, and Procedures

9.1.1 Visit 1, Screening (Days −28 to −1)

Subjects will be screened within 28 days before randomization in the study. The following procedures will be performed at Screening:

- Provide the subject with the informed consent document and explain the rationale for the study, providing ample time for participants and authorized representatives to ask questions. Consent will be obtained before any subsequent screening related procedures are performed.
- Review inclusion/exclusion criteria.
- Review and record: Patient medical/psychiatric history and demographics.
- Review and record: Medications currently being taken or taken within the previous 1 year (5 years in the case of psychiatric drug history) of Screening (including OTC medications, vitamins, and supplements). Determine medication washout requirements and duration. Subjects who are receiving prohibited medications (e.g., antipsychotics, antidepressants, anticonvulsants/mood stabilizers, anxiolytics, and sedatives/hypnotics) except as specifically allowed, will require a washout period. All prohibited medications should be washed out before Visit 2.
- Perform a complete physical examination (excluding breast and genitourinary examination) with review of body systems.
- Record vital signs: Blood pressure, pulse, respiratory rate, and oral temperature after subject has been seated for 5 minutes.
- Measure height and weight.
- Collect blood and urine samples for central clinical laboratory tests (hematology, serum chemistry, urinalysis, thyroid panel, and serum ethanol); see Section 9.3.3.2.1 for a complete list of required laboratory tests.
- Collect urine for an on-site urine drug screen and urine pregnancy test (if female).
- Conduct SCID-5-CT interview to confirm MDD diagnosis.
- Administer evaluations:
    - MADRS (≥ 25 inclusive)
    - CGI-S (≥ 4 inclusive)
    - QIDS-SR-16
    - Columbia – Suicide Severity Rating Scale (C-SSRS) (lifetime)

- [redacted]

9.1.2 Visit 2, Baseline (Day 0)

Subjects will return for Visit 2 up to 28 days after Visit 1. The interval may be extended, if necessary and after discussion with the Axsome Medical Monitor, to accommodate medication washout or repeat screening procedures. The following procedures will be performed at Baseline (Day 0):

- Review and confirm inclusion/exclusion criteria.
- Record vital signs, including: Blood pressure, pulse, respiratory rate, and oral temperature after subject has been seated for 5 minutes.
- Review and record AEs since last visit.
- Review and record any current concomitant medication use (including OTC, vitamins, and supplements).
- Collect urine sample for on-site drug screening and urine pregnancy test (if female).
- [redacted]
- Administer evaluations:
  - MADRS ($\geq$ 25 inclusive)
  - CGI-S ($\geq$ 4 inclusive)
  - QIDS-SR-16
  - C-SSRS (since last visit)
- Randomize subject once it is determined that subject satisfies all of the inclusion and exclusion criteria (on the basis of the screening and baseline assessments described above). Eligible subjects will be randomized sequentially and assigned the corresponding kit number.
- Dispense 1 study drug bottle from the subject assigned kit.
- Instruct subject to begin to dose 1 tablet the following morning for the next three days, on an empty stomach (at least 2 hours pre- or 2 hours post-prandial), orally with water.
- Schedule Visit 3 telephone call for Day 3.
- [redacted].

9.1.3 Visit 3 (Day 3)

The following procedures will be performed via telephone at Visit 3 (Day 3):

- Review and record AEs since last visit.
- Review and record any current concomitant medication use (including OTC, vitamins, and supplements).
- Review study drug compliance and confirm QD dosing for 3 days.
- Instruct subject to begin BID dosing on Day 4 (the day after the call or the day of if calling on Day 4). Confirm doses will be taken at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water.
- [redacted]

9.1.4 Visit 4, 5, 6, and 7 (Days 7, 14, 21, and 28)

The following procedures will be performed at Visits 4 – 7 (Days 7, 14, 21, and 28):

- Record vital signs, including: Blood pressure, pulse, respiratory rate, and oral temperature after subject has been seated for 5 minutes.
- Review and record AEs since last visit.
- Review and record any current concomitant medication use (including OTC, vitamins, and supplements).
- [redacted]
- Collect all unused study drug dispensed at previous visit.
- Assess study drug compliance via drug accountability. Noncompliant subjects may be discontinued.
- Dispense and/or redispense study drug bottle(s) to subject from the previously assigned kit.
- [redacted]
- Administer evaluations:
  - MADRS
  - QIDS-SR-16
  - CGI-S
  - CGI-I
  - C-SSRS (since last visit)
- Remind subject to continue dosing BID at least 8 hours apart, orally on an empty stomach (at least 2 hours pre- or 2 hours post-prandial) with water.
- [redacted]

9.1.5 Visit 8 (Day 42) / Early Termination

The following procedures will be performed at Visit 8 (Days 42) or the Early Termination Visit:

- Record vital signs, including: Blood pressure, pulse, respiratory rate, and oral temperature after subject has been seated for 5 minutes.
- Record weight.
- Review and record AEs since last visit.
- Review and record any current concomitant medication use (including OTC, vitamins, and supplements).
- Perform a physical examination (excluding breast and genitourinary examination) with review of body systems.
- Collect blood and urine samples for central clinical laboratory tests (hematology, serum chemistry, urinalysis, thyroid panel, and serum ethanol); see Section 9.3.3.2.1 for a complete list of required laboratory tests.
- Collect urine for an on-site urine pregnancy test (if female).
- [redacted]

- Collect all unused study drug dispensed at previous visit.
- Assess study drug compliance via drug accountability. Noncompliant subjects may be discontinued.
- [redacted]
- Administer evaluations:
  - MADRS
  - QIDS-SR-16
  - CGI-S
  - CGI-I
  - C-SSRS (since last visit)

9.1.6 Visit 9 (Day 49) / 1-Week Follow-up Phone Call

Visit 9 will be conducted by telephone. Any clinical findings observed during Visit 8 including clinically significant laboratory abnormalities, will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to the study drug. An in-clinic follow-up visit, if one should be necessary, will take place within 30 days of study drug termination.

If a subject is not able to continue treatment with study drug for any reason, he or she will be discontinued from treatment and if possible the procedures as listed in Visit 9 will be completed 1 week after the last dose of study drug.

At Visit 9, the following procedures will be performed:

- Review and record AEs since last visit.
- Review and record any current concomitant medication use (including OTC, vitamins, and supplements).
- Administer C-SSRS (since last visit).

9.2 Study Duration

The study will last up to approximately 11 weeks (including a Screening period up to 4 weeks, 6 weeks of treatment, and a 1-week follow-up period).

9.3 Assessments

The assessments listed below will be administered at the time points specified in the Schedule of Assessments in Section 17.2.

9.3.1.1 Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT)

The SCID-5-CT [9] is a clinician-rated diagnostic assessment that will be administered at Visit 1 and will be considered a source document in this study. The SCID-5 is an interview guide for making DSM-5 diagnoses and has been adapted for use in this protocol. The interview will be administered by the Investigator or a Sub-Investigator who is a psychiatrist, a doctoral or masters level clinical psychologist or a psychiatric nurse with sufficient experience in the diagnosis of mental illness.

9.3.1.2 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS [10] 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.

9.3.1.3 Quick Inventory of Depressive Symptomology – Self-Rated (QIDS-SR-16)

The 16-item QIDS-SR-16 [11], a patient-rated scale, is an abbreviated version of the 30-item Inventory of Depressive Symptomatology (IDS) and is designed to assess the severity of depressive symptoms. The QIDS-SR-16 assesses criterion symptom domains to diagnose a major depressive episode.

The QIDS-SR will be used to assess the subject's depressive symptomatology over the past 7 days. Subjects report severity of symptoms on 10 items assessing sleep, feelings of sadness, appetite, weight change, concentration, self-regard, suicidality, general interest level, energy level, psychomotor retardation, and restlessness. Each item will be scored on a 4-point scale with a score of 0 reflecting no symptoms and a score of 3 reflecting symptoms of maximum severity.

9.3.1.4 Clinical Global Impression – Severity (CGI-S)

The CGI-S scale [12] 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 MDD. 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.

9.3.1.5 Clinical Global Impression – Improvement (CGI-I)

The CGI-I scale [12] 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.

[redacted]

9.3.2 Clinical Pharmacology

[redacted]

9.3.3 Safety

Safety assessments will include the evaluation of TEAEs; clinical laboratory test results; 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 (Section 17.2).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), platelet count (or estimate), and white blood cell count (including differential), absolute and % Neutrophil, Lymphocyte, Basophil, Monocyte, and Eosinophils
Serum Chemistry	Albumin, total bilirubin, direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, random glucose, sodium, potassium, chloride, C-reactive protein (CRP), cholesterol
Urinalysis	pH, specific gravity, blood, glucose, protein, ketones, and leukocyte esterase
Thyroid Panel	TSH, Free T3, Free T4
Urine Drug Screen	Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine, ecstasy (MDMA)
Serum Ethanol Level	
Repeat Urine Drug Screen	May be performed at random during the study upon request of the investigator
Repeat Serum Ethanol Level	May be performed at random during the study upon request of the investigator

Other laboratory assessments may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately follow up and/or manage an adverse experience.

All blood and urine samples will be sent to a central laboratory for analyses.

9.3.3.2.2 Pregnancy Testing

Female subjects will be required to have an onsite urine pregnancy test at Visit 1, Visit 2 and Visit 8/ET.

A positive pregnancy test will exclude a subject from participating further in the study. In the event that a false positive is suspected, a repeat pregnancy test may be performed. Investigators should inquire at every study visit about the continued use of acceptable methods of contraception in

females of child-bearing potential and perform a repeat pregnancy test if there is any question of non-compliance with contraception.

9.3.3.2.3 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 the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The Investigator 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.

9.3.3.2.4 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 or its designee 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 temperature. Seated blood pressure and other vital signs will be measured after the subject has been in a sitting position for 5 minutes.

9.3.3.3.2 Physical Examination

A complete physical examination (excluding breast and genitourinary examination) will be performed at Screening by a licensed physician or clinician (NP, DO, PA) and at the final on-site visit (Visit 8/ET). Physical examination will include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The physical examination should be performed by the same person each time, whenever possible. Physical examination abnormalities determined by the Investigator to be clinically significant at Screening should be recorded as medical history. The thoroughness of the Visit 8/ET physical examination is at the discretion and judgment of the Investigator, but should include a brief review of systems to ensure there have been no changes since Screening.

9.3.3.3.3 Other Safety Assessments

9.3.3.3.3.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS [14] 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.

The C-SSRS will be completed at Visits 1, 2, and 4 – 9. At Visit 1 (Screening) the C-SSRS will be completed for the subject's lifetime history of suicidal ideation and behavior, along with a recent recall period. At all other 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.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject 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.)

Events that occur in subjects treated with active comparator or during treatment-free periods of the study are also considered AEs.

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, instead of "runny nose").

Please note medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

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 "responses to a 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 and in the current package inserts for marketed drugs that contain the same active moiety. 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. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, <u>does not</u> qualify the condition or event 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 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of the study drug and not more than 30 days after the last study visit.

10.2 Management of Adverse Events

Adverse events will be collected from the time of signing the ICF through 30 days after the last study visit or Early Termination, whichever occurs first. Only Serious adverse events will be collected for subjects who screen fail.

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 increased	An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount.
Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
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 CRF completion 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 unrelated 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 test 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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
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 subject 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 CRF 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 and time).
- When the AE stopped (stop date and time 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.

Any time a subject reports an AE that is considered to be serious, he or she should be encouraged to return to the site to be evaluated, which will include having blood and urine samples taken for drug concentrations. Recent dietary information will be collected.

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 blood sample for plasma concentrations of the study drug, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 8.6 for a description of the unblinding procedures.

10.2.5 Follow-up of Adverse Events

Any AE will be followed 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 CRF.

10.2.6 Notification

10.2.6.1 Serious Adverse Events

The Investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event by completing the SAE Report Form and faxing or emailing it to number or email shown below. Axsome's Medical Monitor may also be notified by telephone. Even if an initial report is made by telephone, the SAE Report Form must be completed with all available details and faxed within 24 hours of knowledge of the event at the study site.

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 and initials.
- Subject's date of birth.
- Subject's gender.
- Date of first dose of study drug(s).

- Date of last dose of the study drug(s), if applicable.
- Adverse event term.
- Time and 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).
- Whether and when the Investigator was unblinded as to the subject's treatment assignment.

[redacted]

The Investigator must fax or e-mail a written SAE Report Form that describes the SAE to the recipient(s) of the initial information, who will forward the information to Axsome. The Investigator must also immediately deliver any available supporting information requested on the SAE Report Form or by Axsome.

Any missing or additional relevant information concerning the SAE should be provided to the recipient(s) of the initial information in a written, follow-up SAE Report Form. Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the subject's CRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. Axsome Therapeutics, Inc. may contact the study site to solicit additional information or follow up on the event.

The Investigator is required to comply with applicable regulations (including local laws and guidances) 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 (see the Safety Management Plan). 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 CRFs 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

In the rare chance that a pregnancy occurs or is suspected, women should be instructed to contact the Investigator or study staff immediately.

A woman who becomes pregnant during study drug treatment or within 30 days of discontinuing the study drug will be immediately discontinued from study participation. The Investigator must report the pregnancy as if it were an SAE within 24 hours of learning of the pregnancy. The Investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on a Pregnancy and Lactation Exposure Form/other designated form provided by Axsome or its designee.

Early termination visit assessments are required as soon as possible after learning of the pregnancy. The Investigator is also responsible for following the pregnancy until delivery or termination. Findings must be reported on the Pregnancy and Lactation Exposure Form/other designated form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly. If the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for hemorrhage), a separate SAE Form must be filed with the appropriate serious criterion (e.g., hospitalization) indicated in addition to the aforementioned designated form.

10.3.3 Overdose

The dose of study drug specified in the protocol should not be exceeded during the study.

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

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 other analyses. The final clinical study report will discuss deviations from the SAP, if any.

12.1.1 Safety Endpoints

Safety endpoints include the following:

- Adverse Events (AE)
- Adverse Dropouts (ADOs)
- Incidence of Treatment Emergent Adverse Events (TEAEs)
- Clinical laboratory test results
- Vital sign measurements
- Physical examination findings
- Columbia – Suicide Severity Rating Scale (C-SSRS)

12.2 Sample Size Determination

Approximately 60 subjects (30 per arm), who are compliant and who complete the 6-week treatment period, are planned for this study. The sample was determined based on prior reported experience with trials of a similar stage, in a similar patient population, with a similar objective. A sufficient number of subjects will be screened to achieve the planned number of subjects.

12.3 Analysis Populations

The following 3 analysis populations are planned for this study:

- Modified Intent-to-Treat (mITT) Population—the mITT population and will include data from all subjects who receive at least 1 dose of study drug and provide at least 1 post-Baseline assessment.
- Intent-to-Treat Population—the ITT will include all subjects who are randomized
- Safety Population—the Safety Population will be the primary safety analysis population and will include all subjects who receive at least 1 dose of the study drug.

Membership in the analysis populations will be determined before unblinding.

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 screened, randomized, completing, discontinuing treatment, and withdrawing, along with reasons for discontinuation or withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

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 minors and majors, 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 for each treatment group and for the overall population by descriptive statistics.

12.4.1.4 Medical History and Clinical Laboratory

Medical history and clinical laboratory tests will be listed. Prior and concomitant medications will be summarized by treatment group, 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 dose taken. Descriptive statistics for these quantities, including the mean, SD, minimum, and maximum, will be provided by treatment group.

Overall study drug compliance based on tablet count will be defined as the actual dose taken divided by the intended dose times 100.

12.4.3 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 12.3).

Safety and tolerability will be assessed through TEAEs; hematologic, biochemical, and urinalysis laboratory parameters; physical examination findings; and vital signs measurements.

No formal statistical comparisons will be performed for safety endpoints.

12.4.3.1 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities reporting system. Treatment-emergent AEs are defined as any of the following:

- Non-serious AEs with onset on the date of first dose of treatment with the study drug through follow up (7 days after the last dose of study drug);
- Serious AEs with onset on the date of first dose of treatment with the study drug through 30 days after the last dose of study drug;

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

12.4.3.2 Clinical Laboratory Evaluations

For continuous laboratory parameters, descriptive statistics will be presented for each visit and for the changes from Baseline to each subsequent visit by treatment group.

Additionally, clinical laboratory parameters will be categorized as low, normal, or high according to laboratory range specifications and the number and percentage of subjects in each category will be presented in shift tables.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

12.4.3.3 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, pulse, respiratory rate, and oral temperature.

12.4.3.4 Physical Examination Findings

Physical examination data will be presented in the listings.

12.4.3.5 Other Safety Parameters – C-SSRS

The number and percentage of subjects with suicidal ideation or suicidal behavior based on the C-SSRS will be summarized by treatment group. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the patient's lifetime, during the double-blind treatment period, and during the safety follow-up period will also be presented by treatment group for the Safety Population. Supportive listings will be provided and will include the subject number, study center number, lifetime history, and post-baseline values. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings. A listing of all AEs occurring in subjects who have suicidal ideation or suicidal behavior will also be provided.

[redacted]

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 13.6), 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 17.1), the Investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in 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, 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 or its designee 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 or its designee.
- 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 all Investigators 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 or its designee 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 IB, CRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and study product 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 17.1), the Investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all participating subjects.

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 CRFs used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered on the CRFs according to the completion guidelines provided by Axsome or its designee.

The Investigator will sign off each subject casebook. These signatures serve to attest that the information contained in the CRFs is accurate and true.

13.3.3 Source Documents

All information recorded in the CRFs 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 CRF 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 CRFs (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 or its designee 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 and/or its designee 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:

- Regulatory documents, directly comparing entries in the CRFs with the source documents.
- Consenting procedures.
- AE procedures.

- Storage and accountability of the study drug and study materials.
- Maintenance of study blind.

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting the CRFs are described in the CRF completion guidelines. As representatives of Axsome, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.1), 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 monitors 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.

Study site personnel will be responsible for providing resolutions to all data queries. The Investigator will be required to document 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. The audits will be undertaken to check compliance with GCP guidelines and will include a minimum of:

- In-house study file audit.
- Audit of computer database quality control.
- Audit of clinical report quality control.

Axsome or its designee may conduct additional audits on a selection of study sites, requiring access to 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 or its designee 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, or respective steering committees. 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 have to 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.

13.6 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 Investigators final approval and lock of all subject data, return of unused study material and investigational product unless otherwise provided for in writing by Axsome, and final visits by study monitors.

13.6.1 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 subject clinical source documents.

- The Investigator's study file will contain the protocol and protocol amendments (if applicable), CRF guidelines, CRF query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence.
- Subject clinical source documents (which are usually defined by the project in advance to record key parameters independent of the CRF) may include subject 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 subject's involvement in the study should be clearly documented in the study site's clinical records. Details should include the study protocol number, the subject's screening and randomization number, the subject'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 the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, the Sponsor 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 the Sponsor 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 subject, appropriate copies should be made for storing outside the site.

13.7 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 or 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.

13.8 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. Case report forms 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 Sponsor.

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 clinical study report will be written within 1 year of 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 or 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. Informed consent will be obtained from each subject (if the subject is capable in the judgment of the Investigator to provide informed consent) or the subject's authorized representative. For subjects that are not capable of providing informed consent, but are capable of providing assent, the subject will be asked to provide assent. If the subject is not capable of providing assent, the Investigator will document the reasons why and maintain that documentation with the other informed consent documents. 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 (and 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 and to give them sufficient time to understand the information and to prepare questions before being asked for their consent. The Investigator must confirm that the text was understood by the subject or the subject's authorized representative. Subjects capable of signing consent, or the subject's authorized representative, will then sign and date the IRB/IEC-approved consent form indicating that they have given their consent to participate in the study. The signatures confirm the consents are based on information that has been understood. The forms will also be signed by the Investigator, or designee, obtaining the consents and annotated with the study subject number. Each subject's signed ICFs must be kept on file by the Investigator for possible inspection by regulatory authorities, Axsome, and/or designated personnel. Collection of informed consent has to be documented on the CRF.

Furthermore, the subject will be informed that if they wish 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 names 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 or 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.

Until written approval by the IRB or 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 or IEC. Axsome must receive their written approval before implementation.

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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[4] L. Nguyen, M. J. Robson, J. R. Healy, A. L. Scandinaro and R. R. Matsumoto, "Involvement of sigma-1 receptors in the antidepressant-like effects of dextromethorphan," *PLoS One,* vol. 31, no. 4, pp. 1-9, 2014.

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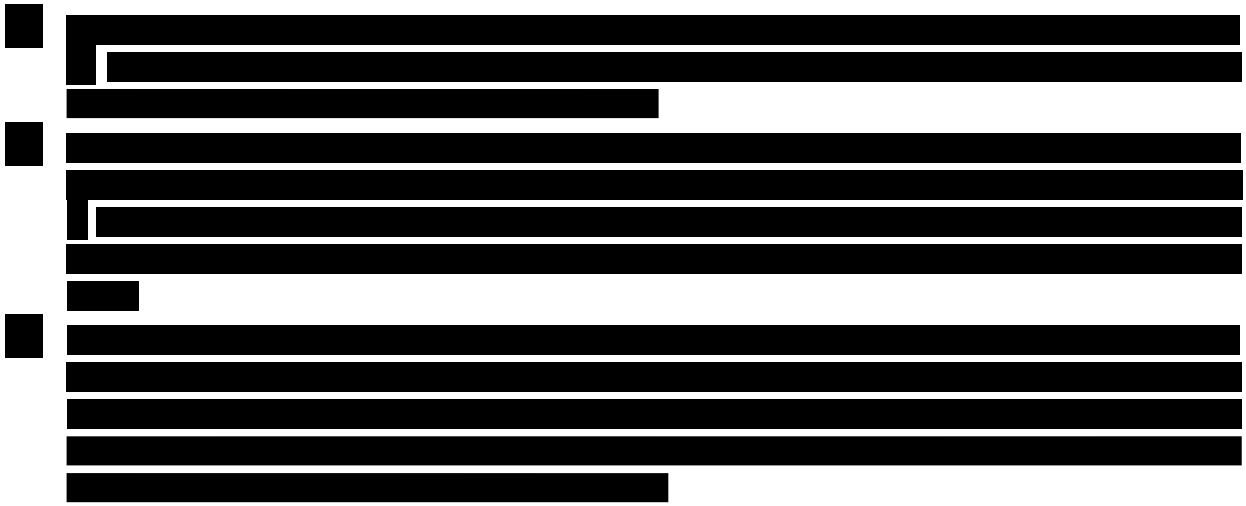

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17. ATTACHMENTS

17.1 Investigator's Agreement

PROTOCOL NUMBER:	AXS-05-MDD-201
PROTOCOL TITLE:	A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects with Major Depressive Disorder
PROTOCOL	Version 2.0: 28Jun2018

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 understand 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: _____

Investigator's site name and address:

_____

_____

_____

17.2 Schedule of Assessments

Visit	Screening Visit 1	Baseline Visit 2	Phone Call Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 / ET	Visit 9 Follow-up[a]
Study Day	**-28 to -1**	**0**	**3 (+1)**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**42 (±2)**	**49 (±2)**
Week	**-4 to -1**			**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 7**
Informed Consent	X[b]								
Inclusion/Exclusion Criteria	X	X							
Demographics	X								
Medical/Psychiatric History	X								
Medication History	X								
Physical Examination	X							X	
Vital Signs, Height/Weight[c]	X	X		X	X	X	X	X	
Laboratory Tests[d]	X							X	
Urine Drug Screen[e]	X	X						X	
Serum Ethanol[e]	X							X	
Urine Pregnancy Test (all female subjects)	X	X						X	
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SCID-5-CT	X								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MADRS	X	X		X	X	X	X	X	
QIDS-SR-16	X	X		X	X	X	X	X	
CGI-S (Severity)	X	X		X	X	X	X	X	
CGI-I (Improvement)				X	X	X	X	X	
C-SSRS	X	X		X	X	X	X	X	X
Randomization		X							
Instruct to begin BID dosing			X						
Study Drug Dispensation[h]		X		X	X	X	X		
Study Drug Accountability			X	X	X	X	X	X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

Abbreviations: SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version; ET = early termination; EOS = End of Study; MADRS = Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self- Rated; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia - Suicide Severity Rating Scale; [redacted]

a Safety follow-up visit to be performed telephonically.
b Informed consent must be signed prior to any study procedures being performed.
c Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a seated position for at least 5 minutes. Height will be measured at Visit 1 and weight at Visit 1 and Visit 8 (EOS or ET).
d Clinical laboratory tests will include hematology, serum chemistry, urinalysis and thyroid panel.
e May be performed at other study visits per investigator judgment. Subjects with positive urine drug screen or serum ethanol levels at Visit 1 may be allowed in study depending on circumstances described to the Medical Monitor and a negative repeat UDS is obtained before Visit 2.
f [redacted]
h Subjects will begin to take study drug the morning of Day 1 (morning after Visit 2).

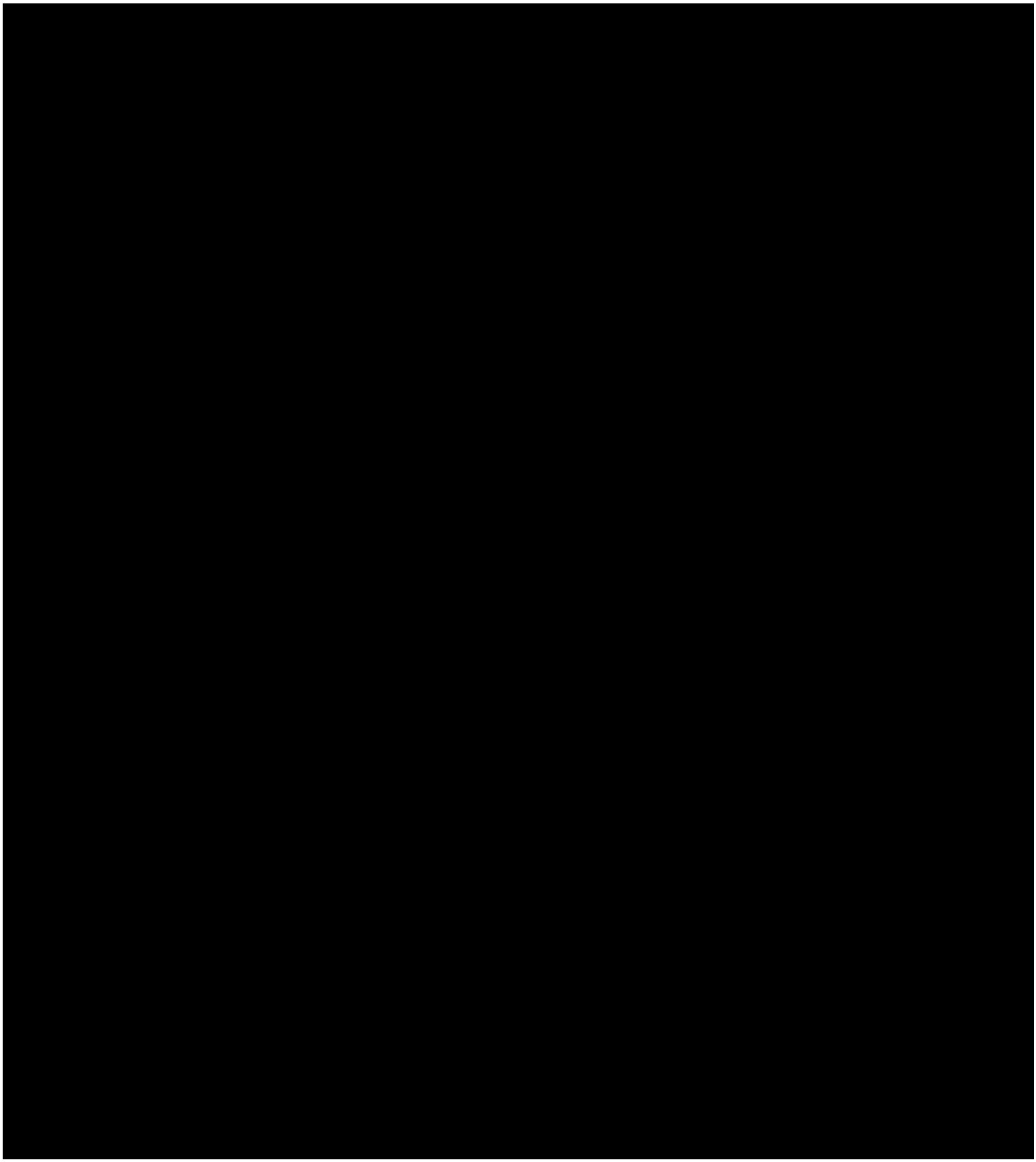
APPENDICES

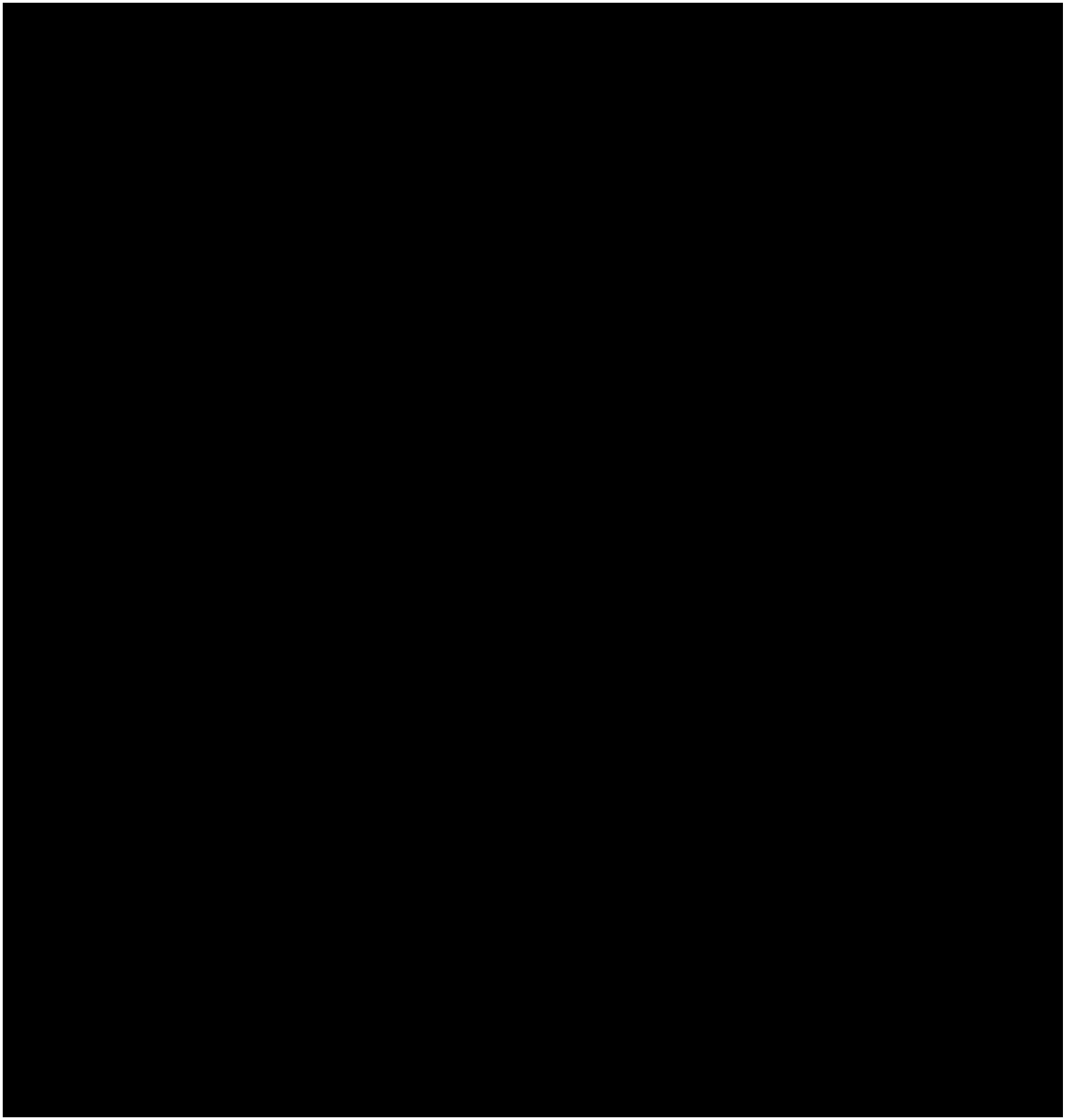
[redacted]

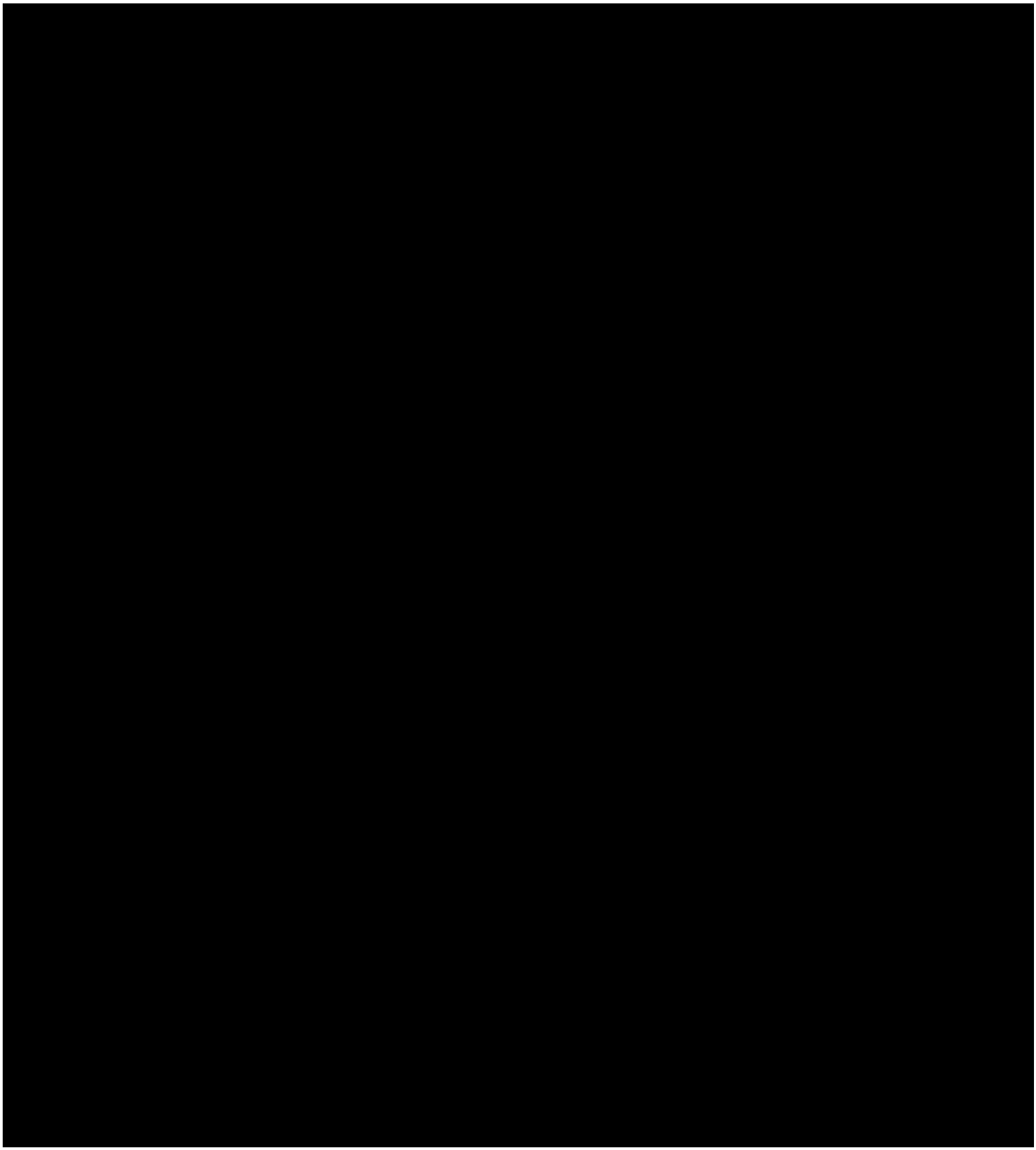
B. Regulations and Good Clinical Practice Guidelines
C. Structured Clinical Interview for DSM-5, Clinical Trials (SCID-5-CT)
D. Montgomery and Åsberg Depression Rating Scale (MADRS)
E. Quick Inventory of Depressive Symptomology – Self-Rated (QIDS-SR-16)
F. Clinical Global Impression of Severity of Illness (CGI-S)
G. Clinical Global Impression of Improvement of Illness (CGI-I)
H. Columbia – Suicide Severity Rating Scale (C-SSRS) – Lifetime
I. Columbia – Suicide Severity Rating Scale (C-SSRS) – Since Last Visit

[redacted]

**Samples of these scales are provided to give the Investigators and IRB(s) an understanding of the content of each of the scales. The final versions used in the clinical trial are subject to changes in layout and formatting as appropriate for each of the validated versions.*







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:
http://www.ich.org/LOB/media/MEDIA482.pdf