CLINICAL STUDY PROTOCOL

A Multicenter, Fixed-Dose, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of AR19 (Amphetamine Sulfate) in Adult Subjects (Ages 18-55) with Attention Deficit Hyperactivity Disorder (ADHD)

Protocol AR19.004

Arbor Pharmaceuticals, LLC.

6 Concourse Parkway, Suite 1800

Atlanta, GA 30328

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IND # 128294

-Confidential-

This clinical study will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, Good Clinical Practices (International Conference on Harmonization Guideline E6), United States Code of Federal Regulations Title 21, and any local and/or federal regulations.

STUDY CONTACTS

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SPONSOR SIGNATURE PAGE

Title: A Multicenter, Fixed Dose, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of AR19 (Amphetamine Sulfate) in Adult Subjects (Ages 18-55) with Attention Deficit Hyperactivity Disorder (ADHD)

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

SIGNATURE

INVESTIGATOR'S STATEMENT

I have read the protocol, and I approve this document. I agree to conduct the study in accordance with the design and specific provision of this protocol and to comply with its obligations, subject to ethical and safety considerations and all applicable regulations (ICH, CFR, and IRB). I will provide copies of this protocol and access to all information furnished by Arbor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential, and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Arbor or by me if it becomes necessary to protect the best interests of the study participants.

Confidentiality Statement

The confidential information in this document is provided to you as a Principal Investigator for review by you, your staff, and the applicable Institutional Review Board. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Principal Investigator:

Name (please print)	Site Number
Title	
Signature	Date

Amendment #1:

Changes made include clarifications on procedures, correction of typographical errors, and removal of PK processing information which will be detailed in the laboratory manual. Modified text is listed here in **bold type.** Specifically:

- Synopsis and Section 4.2:

Exclusion Criteria #9

WAS: Has an ECG or clinical evidence of the following:
- QTcF > 470 milliseconds (msec) for males, and > 450 msec for females

IS: Has ECG or clinical evidence of the following:
- QTcF > 470 milliseconds (msec) for **females**, and > 450 msec for **males**

Exclusion Criteria #12

WAS: Has used prohibited drugs or agents (see Appendix B) within 30 days of the Baseline visit through Study Visit 7. (Stimulant medications are allowed until 7 days before the Baseline visit). Non-stimulant ADHD medications (guanfacine, bupropion, clonidine, and/or atomoxetine) are not allowed within 30 days of Visit 2 or at any time during the study.

IS: Has used prohibited drugs or agents (see Appendix B) within **28** days of the Baseline visit through Study Visit 7. (Stimulant medications are allowed until 7 days before the Baseline visit). Non-stimulant ADHD medications (guanfacine, bupropion, clonidine, and/or atomoxetine) are not allowed within **28** days of Visit 2 or at any time during the study.

Exclusion Criteria #20

WAS: Note: subjects should be informed that they must not drink alcohol within 12 hours of screening and this should be confirmed prior to testing.

IS: Note: subjects should be informed that **alcohol consumed within 12 hours of screening may result in a positive test.**

- Section 5.9.1 Prior Medication

WAS: Has used prohibited drugs or agents (see Appendix B) within 30 days of the Baseline visit through Study Visit 7. (Stimulant medications are allowed until 7 days before the Baseline visit). Non-stimulant ADHD medications (guanfacine, bupropion, clonidine, and/or atomoxetine) are not allowed within 30 days of Visit 2 or at any time during the study.

IS: Has used prohibited drugs or agents (see Appendix B) within **28** days of the Baseline visit through Study Visit 7. (Stimulant medications are allowed until 7 days before the Baseline visit). Non-stimulant ADHD medications (guanfacine, bupropion, clonidine,

and/or atomoxetine) are not allowed within **28** days of Visit 2 or at any time during the study.

- Section 6.1.1 Screening Visit:

WAS: CYP 2D6 genetic testing (analyzed only for randomized subjects who opt in)

IS: **Statement removed** (this procedure is performed at the Baseline Visit)

- Section 11.3 Appendix C:

WAS: Pharmacokinetic sample collection, processing, and shipment instructions with table

IS: **Appendix C removed** (PK collection, processing, and shipment instructions will be detailed in the central laboratory manual)

- Section 6.4.4 Hematology, Serum Chemistry and Urinalysis

WAS: CYP 2D6 genetic testing will be performed only at Screening (Visit 1) for those subjects who opt in. Only randomized subjects who opt in will have their blood tested.

IS: CYP 2D6 genetic testing will be performed only at **Baseline (Visit 2)** for those **randomized subjects who opt in. Subjects who opt out are still eligible for the study.**

SYNOPSIS

Protocol Title	A Multicenter, Fixed-Dose, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of AR19 (Amphetamine Sulfate) in Adult Subjects (Ages 18-55) with Attention Deficit Hyperactivity Disorder (ADHD)
Phase of Development	Phase 3
Investigators/Study Centers	Approximately 30 investigators will enroll subjects at centers in the United States.
Objectives	**Primary Objective:** To assess the efficacy of AR19 compared to placebo using the Adult ADHD Investigator Rating Scale (AISRS) **Secondary Objectives:** • To assess efficacy using AISRS subscale scores • To assess global efficacy using the Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I) • To assess efficacy for treating executive function as measured by the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) • To investigate the safety and tolerability of AR19 in adult subjects ages 18-55 with ADHD **Exploratory Objective** • To assess efficacy for treating emotional dysregulation using established self-rated instruments for emotional dysregulation. To explore which facets of emotional dysregulation change with treatment using item and subscale analyses. • To assess exposure-response relationships using population pharmacokinetics
Planned Number of Subjects	312
Study Design	After Screening and Baseline evaluations are complete, eligible subjects will be randomized 1:1:1 to one of two fixed-dose groups in two divided doses (AR19 20 mg or AR19 40 mg) or placebo. Subjects unable to tolerate AR19 will be withdrawn from the trial. Subjects will begin dosing with double-blind study drug the morning following the Baseline visit. In order to maintain the

blind between the 10 mg and 20 mg capsules, a double-dummy technique will be utilized with matching placebo capsules. The first dose will be taken in the morning and the second dose will be taken 4 to 6 hours later.

Subjects randomized to AR19 20 mg daily will be titrated in a blinded fashion according to the schedule below:

Kit Dispensed at Visit/Day	**First Dose**		**Second Dose**	
Visit 2, Day 1	20 mg Placebo	10 mg	20 mg Placebo	10 mg Placebo
Visit 3, Day 8	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 4, Day 15	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 5, Day 22	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 6, Day 29	20 mg Placebo	10 mg	20 mg Placebo	10 mg

Subjects randomized to AR19 40 mg daily will receive:

Kit Dispensed at Visit/Day	**First Dose**		**Second Dose**	
Visit 2, Day 1	20 mg Placebo	10 mg	20 mg Placebo	10 mg Placebo
Visit 3, Day 8	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 4, Day 15	20 mg	10 mg Placebo	20 mg Placebo	10 mg
Visit 5, Day 22	20 mg	10 mg Placebo	20 mg	10 mg Placebo
Visit 6, Day 29	20 mg	10 mg Placebo	20 mg	10 mg Placebo

Subjects randomized to placebo will receive the 10 mg and 20 mg placebo capsules for the first and second dose for the duration of the trial (four capsules/day).

Visit 7, Day 36: End of Study Visit

Visit 8: Follow-up Phone Call

	Inclusion: 1. Is male or female between 18 and 55 years of age, inclusive, at the time of Screening. 2. Meets criteria for diagnosis of ADHD using Conners' Adult ADHD Diagnostic Interview for DSM-IV™ adapted for DSM-5™ (CAADID). 3. Has an AISRS total score of ≥26 at Visit 2. 4. Has a clinician-administered CGI-S score of 4 or greater at Visit 2. 5. In the clinical judgment of the Investigator, the subject needs pharmacological treatment for ADHD. 6. Must read and write English at a level sufficient to provide written informed consent and to complete study-related materials. 7. For subjects currently on a stable dose of allowed non-ADHD medication, there will be no expected changes in subject's medications during the study with the exception of medications listed in Section 5.9.2. 8. Males and females who are fertile and sexually active with a partner of the opposite sex must adhere to contraception requirements for the duration of the study as follows: o Females of childbearing potential must agree to be abstinent or to use highly effective forms of contraception. o Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study. o Males, including males who are surgically sterile, with female partners of childbearing potential, must agree to be abstinent or else use a medically acceptable form of contraception from screening through the end of study. Exclusion: 1. Has a primary psychiatric diagnosis other than ADHD. 2. Has any other current secondary or co-morbid medical, psychiatric, or social condition which, in the opinion of the investigator, might compromise subject safety, or is likely to interfere with protocol compliance or to confound the assessment of safety or efficacy. 3. Has a history or current symptoms of bipolar disorder,

	schizophrenia or psychotic disorder. 4. Has clinically significant cognitive impairment in the clinical judgment of the Investigator. 5. Has a Body Mass Index of <17 or ≥39 kg/m^2. 6. Has a Screening or Baseline blood pressure of ≥139 mmHg systolic or of ≥89 mmHg diastolic. 7. Is pregnant or breastfeeding, or is planning to become pregnant during the study. 8. Has a history of any of the following disorders: • seizure disorder (excluding a history of isolated febrile seizures <6 years old), • Inadequately or not treated hypertension is defined as a subject who has blood pressure indicative of Stage 2 hypertension (systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg). Subjects who are adequately treated must be on a stable dose of antihypertensive medications for 3 months prior to screening and their antihypertensive medications are not anticipated to change. Blood pressure will be taken in triplicate, and the average will be used for evaluating entry criteria. • Untreated thyroid disease. Subjects with a history of thyroid disease who have been on a stable dose of thyroid hormone for at least three months are eligible to participate if their thyroid-stimulating hormone (TSH) level does not fall in the excluded range, shown below in 14. • Glaucoma • Tourette's disorder, or chronic tics. 9. Has ECG or clinical evidence of the following: • QTcF > 470 milliseconds (msec) for females, and > 450 msec for males • Atrial or ventricular hypertrophy • Intraventricular conduction defects other than incomplete right bundle branch block in the absence of other heart disease • Myocardial infarct, ischemia, or symptomatic coronary artery disease within 1 year prior to the Screening Visit • Clinically significant atrial or ventricular dysrhythmia; the heart must be in predominantly normal sinus rhythm • Second or third degree atrioventricular block • Heart failure

	• Functionally significant cardiac structural abnormality or valvular disease • Cardiomyopathy • Any other cardiovascular condition that the Investigator feels may predispose the subject to cardiovascular events (e.g., myocardial infarction, stroke) or arrhythmia 10. Known family history of sudden cardiac death in the absence of pre-existing heart disease. 11. Use of any psychotropic medication within 30 days of the Baseline visit except for ADHD medication. (Sedative hypnotics prescribed as a sleep aid at a stable dose for at least 30 days prior to Baseline, at bedtime only, are allowed during the study). 12. Has used prohibited drugs or agents (see Appendix B) within 28 days of the Baseline visit through Study Visit 7. (Stimulant medications are allowed until 7 days before the Baseline visit). Non-stimulant ADHD medications (guanfacine, bupropion, clonidine, and/or atomoxetine) are not allowed within 28 days of Visit 2 or at any time during the study. 13. Has received an investigational drug within 60 days of the Screening visit. 14. Has an abnormal laboratory test value, vital sign, or other exam finding at Screening or Baseline that, in the opinion of the Investigator, warrants exclusion from the study. In addition, subjects with laboratory values listed below are considered exclusionary: • Serum aspartate transaminase (AST) or alanine transaminase (ALT) >1.5 × upper limit of normal (ULN) • Serum total bilirubin >1.5 × ULN unless due to Gilbert's Syndrome • Serum creatinine > 1.3 × ULN • Glycosylated hemoglobin (HbA1c) ≥7.0%. • TSH <0.9 × lower limit of normal (LLN) or TSH >1.2 × ULN 15. Reports a history of hypersensitivity or intolerance to any formulation of amphetamine. 16. Reports a history of poor therapeutic response to any formulation of amphetamine or methylphenidate despite a clearly adequate trial (including dose and duration). 17. Is unable to swallow medication in capsule form.

	18. Is unable or unwilling to follow directions of study staff or comply with all the testing and requirements of the protocol. 19. Has a positive urine drug result at Screening (with the exception of current ADHD stimulant therapy, if any). Note: subjects should be informed that they should not participate in the trial or submit to urine drug testing if they are using any controlled or recreational drug (other than a prescribed stimulant for ADHD), and non-use should be confirmed prior to testing. 20. Has a positive blood alcohol level at Screening. Note: subjects should be informed that alcohol consumed within 12 hours of screening may result in a positive test. 21. Has current or known history of drug or alcohol abuse within the past 12 months. 22. Has a history of human immunodeficiency virus (HIV), hepatitis B, or untreated hepatitis C infection. Note: Subjects with a history of hepatitis C infection who have been treated and whose HCV RNA is currently undetectable are not excluded. 23. Has a score of ≥2 for suicidal ideation, or any self-injurious behavior in the past year using the Columbia Suicide Severity Rating Scale at Baseline.
Randomization	Study subjects will be randomized to AR19 or placebo at Study Visit 2.
Treatments	AR19 (amphetamine sulfate) 20 mg or 40 mg or matching placebo daily (4 capsules per day)

Criteria for Evaluation	Change in ADHD symptoms will be assessed using the following: • Adult ADHD Investigator Rating Scale (AISRS) • Clinical Global Impression of Severity (CGI-S) • Clinical Global Impression of Improvement (CGI-I) • Behavior Rating Inventory of Executive Function for Adults (BRIEF-A) • Difficulties in Emotional Regulation Scale (DERS) • Affective Style Questionnaire (ASQ) Safety will be assessed using: • Blood pressure and pulse measurements • Weight • Electrocardiograms (ECGs) • Columbia-Suicide Severity Rating Scale (C-SSRS) • Laboratory assessments • Adverse event monitoring

Statistical Methods	**Sample Size:** Approximately 87 patients per treatment group will provide approximately 90% power to detect a 7.0-point difference in mean change from Baseline to Visit 7 in the AISRS total score between one of the AR19 doses and placebo with a standard deviation of 13.0 and Type I error of 0.025 using a two-sample t test. To account for an approximate 20% dropout rate, a total of 104 subjects will be randomized to each of the three treatment groups for a total of 312 randomized subjects. **Statistical Methods:** All continuous study assessments will be summarized by treatment and time point using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point using frequency counts and percentages. Hypothesis testing, unless otherwise indicated, will be two-sided and performed at the 5% significance level. Full details will be included in a statistical analysis plan (SAP). The primary efficacy endpoint is change from Baseline in AISRS total score at Visit 7. A Bonferroni adjustment will be utilized for the primary efficacy analysis where each AR19 dose will be tested against placebo separately using an alpha

	of 0.025 for each test. No other adjustments for multiplicity will be applied to any other endpoints or comparisons. **Analysis Populations:** Three populations will be defined for data analysis: the Safety Population, the Full Analysis Set Population, and the Per Protocol Population. **Safety Population:** All subjects who are randomized and receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety assessments. Results will be presented "as treated." **Full Analysis Set (FAS) Population:** All subjects who are randomized, receive at least one dose of study medication, and have one or more post-baseline on-treatment primary efficacy assessment(s) will be included in the FAS Population. The FAS Population is the primary analysis population for clinical efficacy. Results will be presented "as randomized." **Per Protocol (PP) Population:** All subjects who are in the FAS population and who do not have any major protocol deviations will be included in the PP Population. The PP Population will be used as a sensitivity analysis for clinical efficacy. **Efficacy Analysis:** <u>Primary:</u> The primary efficacy variable, change from Baseline in AISRS at Visit 7, will be compared between each of the two different AR19 dose groups and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model will include fixed effects for treatment, week, baseline AISRS, and the treatment-by-week interaction. Study week will be included in the model as a categorical variable. Within this model, pairwise comparisons (using least squares [LS] mean contrasts) will be made to compare AISRS at Visit 7 for each AR19 dose level with placebo separately (primary efficacy outcome). Treatments will also be compared at other weeks as secondary analyses. If differences between baseline characteristics exist between the three treatment groups in this comparison, it will be investigated whether adjustment for these characteristics is

	clinically relevant and necessary as a sensitivity analysis. <u>Secondary and Exploratory:</u> The number and percentage of subjects who have each category of the CGI-S and CGI-I at each time point will be presented by treatment group. Cochran-Mantel-Haenszel row mean score tests will be used to compare the treatment groups. CGI-S and CGI-I results will also be summarized treating the responses as continuous values. A MMRM will be utilized to compare treatments at each time point. The model will include fixed effects for treatment, week, and the treatment-by-week interaction. BRIEF-A, DERS, and ASQ scale scores will be summarized descriptively over time utilizing observed and change from baseline scores. Treatments will be compared at each time point utilizing MMRM models on change from baseline scores. The model will include fixed effects for treatment, week, baseline value, and the treatment-by-week interaction. **Safety Analysis:** The nature, frequency, and severity of adverse events, including serious adverse events and adverse events leading to discontinuation, will be summarized descriptively by treatment group. Vital signs, ECGs, and clinical laboratory test results will be summarized using actual and change from baseline values. C-SSRS data will be listed.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of Term
ADHD	Attention Deficit Hyperactivity Disorder
AISRS	Adult ADHD Investigator Rating Scale
AE/SAE	Adverse Event/Serious Adverse Event
ASQ	Affective Style Questionnaire
BL	Baseline
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Version
CAADID	Conners' Adult ADHD Diagnostic Interview for DSM-IV™
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CNS	Central Nervous System
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DERS	Difficulties in Emotional Regulation Scale
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IR	Immediate Release
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
MINI	Mini International Neuropsychiatric Interview for Adults
PFC	Prefrontal Cortex
MMRM	Mixed Model for Repeated Measures
SAP	Statistical Analysis Plan
ULN	Upper Limit of Normal

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1 INTRODUCTION

1.1 Background

1.1.1 Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder which typically presents in childhood. As defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5™), ADHD is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity which begin in childhood.[1] ADHD often persists into adulthood with one-half to two-thirds of child patients continuing to be symptomatic adults. The estimated prevalence of ADHD in adults in the United States is 4.4%.[2] ADHD causes significant impairment in patients throughout the lifespan. Adults with ADHD are more likely to quit a job or be fired, have auto accidents, experience sudden changes in personal or career goals, and have higher perceived social and emotional stress.[3,4]

Specific etiology of this disorder is unknown, and there is no single diagnostic test. It is apparent that the prefrontal cortex (PFC) plays a significant role in maintaining executive function, and that patients with ADHD appear to have less-than-adequate PFC activity, resulting in an overall inability to regulate impulsive behavior.[5] Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-5™ characteristics.

The core symptoms used to diagnose ADHD in adults are inattention and hyperactivity-impulsivity. It has, however, been recognized for decades that many adult ADHD patients experience clinically significant levels of emotional dysregulation.[6] Items pertaining to emotional dysregulation are contained in certain domains of several existing tools, including the Behavior Rating Inventory of Executive Function—Adult Version (BRIEF-A), Difficulties in Emotion Regulation Scale (DERS), and Affective Style Questionnaire (ASQ).[7,8,9]

1.1.2 Overview of Current ADHD Treatments

Controlled clinical trials have consistently demonstrated that stimulants (amphetamine and methylphenidate) substantially reduce the characteristic symptoms and functional impairment of patients with ADHD.[10,11] Stimulants have a large effect size, with a mean of 0.73 to 0.96 in placebo-controlled adult ADHD trials.[12]

Amphetamine and methylphenidate both contain chiral centers that give rise to distinct enantiomeric forms. Amphetamine, in particular, exists as dextro- and levo-amphetamine isomers that have different pharmacokinetic and neuropharmacological properties. Several products have been marketed containing different proportions of each isomer. Dexedrine, for example, consists of pure d-amphetamine; while mixed amphetamine salts such as Adderall consist of a ratio of approximately 3:1 d-amphetamine to l-amphetamine.

Benzedrine, a product first marketed in 1933, consisted of a racemic mixture of approximately 50% d-amphetamine and 50% l-amphetamine.

Evekeo® is a marketed immediate-release (IR) formulation of amphetamine sulfate indicated for narcolepsy, ADHD, and exogenous obesity.[13] Amphetamine is a sympathomimetic amine with central nervous system (CNS) stimulant activity and is a 1:1 racemic mix of d-amphetamine and l-amphetamine. The l-isomer is more potent than the d-isomer in cardiovascular activity but less potent in causing CNS excitatory effects.

In response to the growing misuse of amphetamines, including by intranasal administration, AR19 is an abuse-deterrent formulation of a 1:1 racemic mixture of d- to l-amphetamine sulfate.[14,15] Enhancements to the current IR formulation of Evekeo® are intended to achieve a level of deterrence against abuse when the formulation is manipulated and administered by unintended routes (e.g., intranasal, intravenous). The abuse-deterrent capabilities of AR19 are attributed to pellets within the capsule that confer abuse-deterrent properties.

[redacted].

1.1.3 Rationale for Development of AR19 in ADHD Adults

Racemic amphetamine was the first stimulant studied for treatment of behavioral disorders in children in 1937.[16] However, only one study has been conducted to date documenting the efficacy of a 50% d-amphetamine and 50% l-amphetamine compound (Evekeo®) in the treatment of ADHD.

This study was conducted in children ages 6 to 12 years and demonstrated efficacy beginning at 45 minutes and continuing through 10 hours after administration of a single dose.[17] No studies evaluating the effects of this mixture of d:l amphetamine have been completed in adults. The current study will test the safety and efficacy of this composition (AR19) in adult subjects 18 through 55 years old with ADHD.

1.2 Mechanism of Action

Amphetamine is a CNS stimulant. The mode of therapeutic action in humans is not completely understood. Amphetamine is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.[18]

1.3 Rationale for Dose Selection

AR19 will be available in 10 mg and 20 mg strengths for this study.

Although there is limited information regarding dosing of amphetamine-based IR products in adults, the Food and Drug Administration (FDA) has approved several extended-release amphetamine-based products for the treatment of ADHD in adults.[19,20]

In the Evekeo® children classroom study, the median optimized daily dose was 20 mg. In general, adults have lower systemic exposure to amphetamines when receiving the same fixed dosage and formulation.[21]

For one longer-acting amphetamine mixed salt formulation, the maximum dosage was 50 mg (31.3 mg amphetamine equivalents).[20] The maximum daily dose of 40 mg that will be used in this study has 29.3 amphetamine equivalents. AR19 is a 50-50 mixture of d- and l-amphetamine, it is anticipated that the side effect profile of the 40 mg dose should not be substantially greater. Therefore, the 20 and 40 mg daily doses used in this study are expected to show efficacy and establish the safety profile of AR19 in adults.

AR19 will be given twice daily: the first dose on awakening and the second dose four to six hours later. The double-dummy technique will be utilized in order to maintain the blind between the 10 mg and 20 mg capsules and matching placebo.

In adults, the starting dose will be 10 mg once daily the first week and 10 mg twice per day the second week. In subsequent weeks, subjects randomized to 10 mg twice per day (20 mg daily) will remain on that dose until the final visit, while subjects randomized to 20 mg twice per day will be raised in increments of 10 mg/week with completion of titration at Visit 5 (Week 4) and remain on their randomized dose (40 mg/day) for the final visit. Subjects who experience unacceptable tolerability will be discontinued.

The efficacy and safety profile of amphetamine is well established, and recent studies continue to support the safe and effective use of amphetamine for the treatment of ADHD.

The use of amphetamine in the treatment of ADHD is endorsed by professional medical organizations including the National Institute for Health and Care Excellence and the European Network Adult ADHD.[22,23]

There are no published professional guidelines for the treatment of adult ADHD by professional organizations in the United States.

Evekeo® is indicated for children and adolescents 3 years and older. The most common side effects in the Medication Guide include headache, stomach pain, insomnia, decreased appetite, dry mouth, nervousness, and dizziness. For a full list of side effects, refer to the Evekeo® label and Medication Guide.[13]

The most commonly reported adverse reactions from placebo-controlled trials of two extended-release amphetamine-based products in adults with incidence greater than or equal to 5% and at least twice the incidence of placebo included decreased appetite, decreased weight, nausea, dry mouth, diarrhea, insomnia, anxiety, anorexia, dizziness, increased heart rate, and tachycardia.[19,20]

Amphetamine should be given cautiously to subjects with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult

cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.[13]

Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for bipolar disorder is recommended prior to stimulant use. Patients beginning treatment for ADHD should be monitored for the appearance or worsening of aggressive behavior or hostility.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of AR19 compared to placebo using the Adult ADHD Investigator Rating Scale (AISRS).

2.2 Secondary Objectives

- To assess efficacy using AISRS hyperactive and inattentive subscale scores
- To assess global efficacy using the Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I)
- To assess efficacy for treating executive function as measured by the BRIEF-A
- To investigate the safety and tolerability of AR19 in adult subjects ages 18 through 55 with ADHD

2.3 Exploratory Objective

- To assess efficacy for treating emotional dysregulation using established self-rated instruments for emotional dysregulation. To explore which facets of emotional dysregulation change with treatment using item and subscale analyses.
- To assess exposure-response relationships using population pharmacokinetics

3 INVESTIGATIONAL PLAN

3.1 Description of Overall Study Design and Plan

This randomized, fixed-dose, double-blind, multi-center trial investigates the safety and efficacy of AR19 in the treatment of ADHD in adults from 18 through 55 years of age.

Safety parameters and therapeutic effect will be evaluated throughout the trial.

Subjects will be randomized to 20 or 40 mg AR19 daily or placebo in a 1:1:1 ratio in this fixed dose study. The expected drop-out rate is projected at 20%.

The study will consist of:

- A 30-day Screening period and Baseline evaluation

- Titration with AR19 for 4 weeks to 20 or 40 mg daily dose or placebo
- At least two weeks at a stable dose of AR19 or placebo
- Post Withdrawal Follow Up phone call at Visit 8

Study visits will be conducted according to the Schedule of Assessments (Table 6.1.1).

Subjects who have signed an informed consent form (ICF) and who satisfy the inclusion/exclusion criteria will receive study drug twice daily, once in the morning and again four to six hours later. Study medication dosing will start at 10 mg/day and will be titrated in weekly intervals in 10-mg increments to 20 or 40 mg/day, depending on randomization.

It is anticipated that approximately 30 sites will participate in the study. Subject enrollment will continue until approximately 312 subjects are enrolled.

3.2 Endpoints

3.2.1 Efficacy Endpoints

The primary efficacy endpoint is the change in the AISRS total score at Visit 7 compared to Visit 2 (Baseline) with AR19 vs placebo.

Secondary efficacy endpoints include the change in AISRS subscale scores (Inattention subscale and Hyperactivity/Impulsivity subscale), CGI-S, CGI-I, and executive function as measured by the BRIEF-A.

3.2.2 Safety Endpoints

All subjects who enter the study will be assessed for safety. Safety will be monitored by adverse events (AEs) assessed at each visit. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS)[24] will be administered at Baseline and all subsequent scheduled visits to assess emergent suicidal thoughts or behaviors. Medical history will capture all medical conditions at Visits 1 (Screening) and 2 (Baseline). Physical examinations and clinical laboratory tests will be conducted at Screening and at Visit 7 (End of Study) and also can be conducted at any subsequent visit as deemed necessary by the Principal Investigator. Safety will be assessed by the following measures throughout the study:

- Vital sign changes
- Changes in weight
- Incidence and severity of AEs
- Incidence of clinically significant changes from Baseline in the C-SSRS
- Electrocardiogram (ECG) changes
- Laboratory values

3.2.3 Exploratory Endpoints

Items pertaining to emotional dysregulation are contained in certain domains of several existing tools, including the BRIEF-A, DERS, and ASQ, which will be used in this study. We hypothesize that AR19 treatment will improve emotional dysregulation based on prior

studies of stimulant medications. In addition to assessing efficacy, as indicated by the total scores on each instrument, which facets of emotional dysregulation change with treatment using item and subscale analyses will also be explored.

In addition, exposure-response relationships will be explored using population pharmacokinetics.

4 STUDY POPULATION

Approximately 312 adult subjects (male or female) with a diagnosis of ADHD per DSM-5™ criteria will be enrolled. Subjects must be 18 to 55 years old, inclusive, at the time of Screening.

Subjects who satisfy the inclusion/exclusion criteria will undergo a 7-day washout of previous ADHD stimulant medications, and AR19 or placebo will then be initiated at 10 mg/day the morning after Visit 2. Depending on treatment group, the daily dose will be increased in 10-mg increments every week to 20 or 40 mg/day. The study duration from first dose of study drug to the follow-up visit is expected to be approximately 6 weeks.

Subjects will be monitored for safety and for therapeutic response to AR19 treatment. Safety and clinical response assessments will be performed at each visit or more frequently if clinically indicated.

Each subject must meet all the inclusion criteria and none of the exclusion criteria to be eligible for enrollment in the study. Waivers to inclusion/exclusion criteria will **NOT** be granted.

4.1 Inclusion Criteria

A subject may be enrolled in the study if he/she meets all the following criteria:

1. Is male or female between 18 and 55 years of age, inclusive, at the time of Screening.
2. Meets criteria for diagnosis of ADHD using Conners' Adult ADHD Diagnostic Interview for DSM-IV™ adapted for DSM-5™ (CAADID).
3. Has an AISRS total score of ≥26 at Visit 2.
4. Has a clinician-administered CGI-S score of 4 or greater at Visit 2.
5. In the clinical judgment of the Investigator, the subject needs pharmacological treatment for ADHD.
6. Must read and write English at a level sufficient to provide written informed consent and to complete study-related materials.
7. For subjects currently on a stable dose of allowed non-ADHD medication, there will be no expected changes in subject's medications during the study with the exception of medications listed in Section 5.9.2.
8. Males and females who are fertile and sexually active with a partner of the opposite sex must adhere to contraception requirements for the duration of the study as follows:
    - Females of childbearing potential must agree to be abstinent or to use highly effective forms of contraception.

- Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- Males, including males who are surgically sterile, with female partners of childbearing potential, must agree to be abstinent or else use a medically acceptable form of contraception from screening through the end of study.

4.2 Exclusion Criteria

A subject will be excluded from study participation if he/she meets one or more of the following criteria:

1. Has a primary psychiatric diagnosis other than ADHD.
2. Has any other current secondary or co-morbid medical, psychiatric, or social condition which, in the opinion of the investigator, might compromise subject safety, or is likely to interfere with protocol compliance or to confound the assessment of safety or efficacy.
3. Has a history or current symptoms of bipolar disorder, schizophrenia, or psychotic disorder.
4. Has clinically significant cognitive impairment in the clinical judgment of the Investigator.
5. Has a Body Mass Index of <17 or ≥39 kg/m^2.
6. Has a Screening or Baseline blood pressure of ≥139 mmHg systolic or ≥89 mmHg diastolic.
7. Is pregnant or breastfeeding, or is planning to become pregnant during the study.
8. Has a history of any of the following disorders:
   - seizure disorder (excluding a history of isolate febrile seizures <6 years old),
   - Inadequately or not treated hypertension is defined as a subject who has blood pressure indicative of Stage 2 hypertension (systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg). Subjects who are adequately treated must be on a stable dose of antihypertensive medications for 3 months prior to screening and their antihypertensive medications are not anticipated to change. Blood pressure will be taken in triplicate, and the average will be used for evaluating entry criteria.
   - Untreated thyroid disease. Subjects with a history of thyroid disease who have been on a stable dose of thyroid hormone for at least three months are eligible to participate if their thyroid-stimulating hormone (TSH) does not fall in the excluded range, shown below in 14.
   - Glaucoma
   - Tourette's disorder, or chronic tics.
9. Has ECG or clinical evidence of the following:
   - QTcF > 470 milliseconds (msec) for females, and > 450 msec for males
   - Atrial or ventricular hypertrophy

- Intraventricular conduction defects other than incomplete right bundle branch block in the absence of other heart disease
- Myocardial infarct, ischemia, or symptomatic coronary artery disease within 1 year prior to the Screening Visit
- Clinically significant atrial or ventricular dysrhythmia; the heart must be in predominantly normal sinus rhythm
- Second or third degree atrioventricular block
- Heart failure
- Functionally significant cardiac structural abnormality or valvular disease
- Cardiomyopathy
- Any other cardiovascular condition that the Investigator feels may predispose the subject to cardiovascular events (e.g. myocardial infarction, stroke) or arrhythmia

10. Known family history of sudden cardiac death in the absence of pre-existing heart disease.
11. Use of any psychotropic medication within 30 days of the Baseline visit except for ADHD medication. (Sedative hypnotics prescribed as a sleep aid at a stable dose for at least 30 days prior to Baseline, at bedtime only, are allowed during the study.)
12. Has used prohibited drugs or agents (see Appendix B) within 30 days of the Baseline visit through Study Visit 7. (Stimulant medications are allowed until 7 days before the Baseline visit.) Non-stimulant ADHD medications (guanfacine, bupropion, clonidine, and/or atomoxetine) are not allowed within 30 days of Visit 2 or at any time during the study.
13. Has received an investigational drug within 60 days of the Screening visit.
14. Has an abnormal laboratory test value, vital sign, or other exam finding at Screening or Baseline that, in the opinion of the Investigator, warrants exclusion from the study. In addition, subjects with laboratory values listed below are considered exclusionary:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) >1.5 × upper limit of normal (ULN)
    - Serum total bilirubin >1.5 × ULN unless due to Gilbert's Syndrome
    - Serum creatinine >1.3 × ULN
    - Glycosylated hemoglobin (HbA1c) ≥7.0%.
    - TSH <0.9 × lower limit of normal (LLN) or TSH >1.2 × ULN
15. Reports a history of hypersensitivity or intolerance to any formulation of amphetamine.
16. Reports a history of poor therapeutic response to any formulation of amphetamine or methylphenidate despite a clearly adequate trial (including dose and duration).
17. Is unable to swallow medication in capsule form.
18. Is unable or unwilling to follow directions of study staff or comply with all the testing and requirements of the protocol.
19. Has a positive urine drug result at Screening (with the exception of current ADHD stimulant therapy, if any). Note: subjects should be informed that they should not

participate in the trial or submit to urine drug testing if they are using any controlled or recreational drug (other than a prescribed stimulant for ADHD), and non-use should be confirmed prior to testing.

20. Has a positive blood alcohol level at Screening. Note: subjects should be informed that alcohol consumed within 12 hours of screening may result in a positive test.
21. Has current or known history of drug or alcohol abuse within the past 12 months.
22. Has a history of human immunodeficiency virus (HIV), hepatitis B, or untreated hepatitis C infection. Note: subjects with a history of hepatitis C infection who have been treated and whose HCV RNA is currently undetectable are not excluded.
23. Has a score of ≥2 for suicidal ideation, or any self-injurious behavior in the past year using the Columbia Suicide Severity Rating Scale at Baseline.

4.3 Removal of Subjects from Therapy or Assessment

Any subject who withdraws from the study prior to completing the treatment period will be considered to have "prematurely discontinued" study participation. Subjects may withdraw or be withdrawn from the study for the following reasons:

- The subject wishes to discontinue study participation
- An adverse event or serious adverse event that imposes an unacceptable risk to the subject's health to continue in the study
- Major protocol deviations (e.g. failed to meet entry criteria, did not adhere to protocol requirements and/or impact integrity of subject level data)
- The subject is unable to tolerate 20 or 40 mg daily dose, depending on randomization
- Lost to follow up
- The subject becomes pregnant. If subjects are to withdraw due to pregnancy, the procedures in Section 7.6 should be followed
- The sponsor decides to terminate the study.

Although a subject is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights. The procedures described for Early Termination (Section 6.1.5) will be performed, if possible. Every effort will be made to contact a subject who fails to attend a study visit, or does not respond by telephone, to ensure that the subject is in satisfactory health. The Medical Monitor will be informed of removal or early withdrawal of a subject from the study.

Withdrawn subjects will not be replaced.

If modifications in the experimental design, dosages, subject selection, etc. are indicated or required, such changes will be instituted only following consultation between the Sponsor and the Investigator and will be accomplished through formal amendments to this protocol and approval by the appropriate review committees.

This study may be discontinued at any time if, in the opinion of the Principal Investigator or the Sponsor, continuation of the study represents a significant medical risk to participating subjects.

Arbor retains the right to terminate the study at an individual study site or at all study sites for administrative reasons such as, but not limited to: unacceptable subject accrual, failure of the Principal Investigator to conduct the study according to protocol, or failure to complete study case report forms (CRFs) or maintain study records satisfactorily.

5 CLINICAL TRIAL MATERIALS

5.1 Description of Clinical Trial Material

It is the responsibility of the Sponsor to ensure that study drug provided for this study is manufactured under Good Manufacturing Practices (GMP) and is suitable for human use. AR19 contains amphetamine sulfate, which is a white crystalline powder that is freely soluble in water. AR19 has a molecular weight of 368.49 and is provided as 10 mg and 20 mg capsules in this study. Each capsule also contains the following inactive ingredients: polyethylene oxide, polyethylene glycol, starch, citric acid, α-tocopherol, hypromellose, water, and talc. Placebo is identical to AR19, except it contains no active medication.

The following will be supplied by the Sponsor:

- 10 mg and 20 mg AR19 capsules
- Placebo capsules identical in appearance to AR19 at both dosage levels

Arbor will provide sufficient quantities of AR19 and matching placebo to allow for completion of the study. The lot numbers and expiration dates of the study medications will be recorded in the final study report.

Records will be maintained indicating the receipt and dispensation of all medication supplies. At the conclusion of the study, all unused study medication will be returned to the Sponsor's designee for destruction.

5.2 Packaging, Storage, and Dispensing of Study Drug

AR19 and placebo will be provided as capsules in weekly blister cards in blinded packaging. Since AR19 10 mg and 20 mg strengths are two different colored capsules, the double-dummy technique will be utilized to maintain the blind. Double-blinded AR19 and placebo at each dose level will have identical appearance and taste. Each weekly blister card will contain a total of 36 capsules to have a 7-day supply plus 2 extra days.

The placebo is made of pharmaceutical excipients in capsule form. Placebo capsules are identical in formulation, taste, and appearance to AR19, but lack the active ingredient amphetamine sulfate.

Study drug labels will contain information to meet the applicable regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions at room temperature between 68˚F to 77˚F (20˚C to 25˚C), as defined in the United States Pharmacopeia (USP). Until dispensed to the subject, the study drug will be stored in a securely locked area, accessible to authorized personnel only. Study drug contains

amphetamine sulfate, a Schedule II federally controlled substance, and should be stored in accordance with federal, state, and local regulations.

The dispensing pharmacist or designated qualified individual will be responsible for dispensing study drug and documenting important information on the appropriate drug accountability records at the time of dispensing, such as but not limited to: date dispensed, number of capsules, medication identifier or batch number, and subject identification number. The dispensing pharmacist or designated qualified individual will be responsible for providing the subject with the correct blister card in the appropriate strength(s).

Arbor Pharmaceuticals or designee will provide detailed dispensing instructions prior to study conduct.

5.3 Administration

The following dosing procedures will be followed:

- The dosing regimen will be two capsules twice daily. All subjects will be instructed to take their first dose (two different colored capsules) of study medication in the morning. The second dose (two different colored capsules) should be taken four to six hours later.
- Study medication will be administered orally by swallowing the capsules.
- Study drug can be taken with or without food.

This study is a fixed dose regimen. Dose adjustments are not allowed during the study.

After Screening and Baseline evaluations are complete, eligible subjects will be randomized 1:1:1 to one of two fixed-dose groups (AR19 10 mg p.o. b.i.d. or AR19 20 mg p.o. b.i.d.) or placebo.

Subjects unable to tolerate their AR19 dose at any time during study drug administration will be withdrawn from the trial.

Subjects will begin dosing with double-blind study drug the morning following the Baseline visit. The first dose will be taken in the morning (2 capsules) and the second dose (2 capsules) will be taken 4 to 6 hours later.

Table 5.3.1 Titration Scheme for 20 mg Daily Dose

Kit Assigned on Visit/Day	First Dose		Second Dose	
Visit 2, Day 1	20 mg Placebo	10 mg	20 mg Placebo	10 mg Placebo
Visit 3, Day 8	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 4, Day 15	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 5, Day 22	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 6, Day 29	20 mg Placebo	10 mg	20 mg Placebo	10 mg

Table 5.3.2 Titration Scheme for 40 mg Daily Dose

Kit Assigned on Visit/Day	First Dose		Second Dose	
Visit 2, Day 1	20 mg Placebo	10 mg	20 mg Placebo	10 mg Placebo
Visit 3, Day 8	20 mg Placebo	10 mg	20 mg Placebo	10 mg
Visit 4, Day 15	20 mg	10 mg Placebo	20 mg Placebo	10 mg
Visit 5, Day 22	20 mg	10 mg Placebo	20 mg	10 mg Placebo
Visit 6, Day 29	20 mg	10 mg Placebo	20 mg	10 mg Placebo

Subjects randomized to placebo will receive the 10 mg and 20 mg placebo capsules for the first and second dose (4 capsules/day) during the trial.

Visit 7, Day 36: End of Study Visit

Visit 8: Follow-up Phone Call

5.4 Randomization and Blinding Procedures

All study medication will be supplied in weekly blister packs and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

Enrollment will occur at Visit 2, upon randomization, after all screening procedures have been performed and eligibility for the study is confirmed at the Baseline Visit.

For the randomization of subjects, the Investigator or delegated designee will complete the randomization electronic case report form (eCRF), which is integrated with the study interactive web response system (IWRS). The IWRS will assign subjects to a treatment group (placebo, 20 mg, or 40 mg AR19/day) based on the pre-defined randomization list.

Randomization will occur via IWRS at Visit 2, if a subject meets all inclusion and no exclusion criteria. Subjects will be randomized 1:1:1 to placebo or 20 or 40 mg AR19/day. Randomization will take place according to a fixed schedule using a permuted block design with no stratification by clinical site.

5.5 Emergency Unblinding of a Randomization Code

Unblinding should occur only when knowing the treatment assignment has a bearing on the medical treatment or evaluation of a subject. Whenever possible, the need to unblind should be discussed with the Medical Monitor prior to unblinding. In the event of an emergency, the Investigator, Pharmacist, or designated qualified individual may obtain the subject's blinded treatment via IWRS. If an individual designated to perform emergency unblinding does not have access to the IWRS, Sponsor designee may be contacted and can perform the unblinding for that individual.

A subsequent written report, including all pertinent details, must be submitted to the Medical Monitor within 1 business day of the unblinding. Whenever possible, the blind of the subject should be maintained.

If an Investigator, site personnel performing assessments, or subject is unblinded, the subject must be withdrawn from the study, and procedures accompanying withdrawal should be performed.

5.6 Study Drug Adjustments

Subjects who cannot tolerate their daily dose of AR19 (up to 20 or 40 mg daily) will be discontinued from the study. Study drug dose adjustments are not allowed during this fixed dose study.

5.7 Drug Accountability

The Investigator or designee will verify and acknowledge receipt of study drug. All study medication must be stored in a secure area under the proper storage requirements with limited access (i.e., restricted to the Investigator or designees). Study medication designated for this clinical study must not be taken by anyone other than those enrolled in this specific investigation and may not be utilized for any laboratory or animal research. All study medication dispensed to subjects must be accurately recorded on the Drug Accountability Record maintained at the study center. Subjects should be instructed to return all study medication dispensed to them (including any unused capsules and blister cards) at each study visit.

Drug accountability will be performed at each study visit starting with Study Visit 3. At each visit, subjects should return all unused medication dispensed to them at the prior visit. All study medication and blister cards will be retained at the site for study monitor

verification. All study medication should be stored at the study site until further instruction from the study monitor.

The Investigator is responsible for returning all unused or partially used study medication to the Sponsor's designee at the end of the study. The Investigator must verify that all unused or partially used study medication supplies have been returned by the subject and that no remaining supplies are in the Investigator's possession at the time of study discontinuation.

Arbor or designee will provide detailed drug accountability instructions at the start of the study.

5.8 Treatment Compliance

Subject training at the Baseline Visit (Visit 2) and subsequent ongoing retraining regarding proper dosing of study medication will occur to ensure subject compliance. Beginning with Visit 3, study staff will assess compliance at every study visit to confirm that the subject is taking study medication according to the protocol. Compliance is defined as taking 80% to 100% of study medication for the duration of the study.

5.9 Prior, Concomitant, and Prohibited Medications

5.9.1 Prior Medications

Subjects who were taking a prescription psychotropic medication other than a stimulant or sedative hypnotic at the time of Screening are not eligible for the study. Subjects who have recently taken prescription psychotropic medications for ADHD (except stimulants or sedative hypnotics) are eligible, if the psychotropic medication will be discontinued at least 28 days prior to the Baseline Visit. Any non-study ADHD stimulant medication must be discontinued at least 7 days prior to the Baseline Visit 2. Subjects must not have participated in any other clinical study in which an investigational drug was administered within 60 days of the Screening Visit and must not participate in other investigational trials during this study.

5.9.2 Concomitant Therapy

Information on concomitant medications will be collected at each study visit through the Post Withdrawal Follow-Up Phone Call (Visit 8) or early termination.

Intermittent use of acetaminophen or non-steroidal anti-inflammatory medications is allowed. Use of non-sedating antihistamines, including Zyrtec, Claritin, and Allegra, as well as Nasonex will also be allowed during the trial. Acetaminophen is permitted for control of fever or pain, if needed. Short courses of prescription and non-prescription medications for treatment of acute illnesses such as the common cold, viral illnesses, and ear infections are permitted, provided they do not contain the medications listed in Appendix B of the protocol.

If a subject discontinues from the study early, study drug is to be discontinued for at least 24 hours prior to his/her beginning new ADHD therapy.

5.9.3 Prohibited Medications

Use of psychotropic medications, including but not limited to anticonvulsant, antidepressant, anxiolytic, and antipsychotic medications, is not allowed during the study, except for sedative hypnotics used at a stable dose at bedtime only, for at least 30 days prior to Baseline Visit 2. Stimulants (other than study drug) must be discontinued 7 days prior to Baseline Visit 2. Non-stimulant ADHD medications (guanfacine, bupropion, clonidine, and/or atomoxetine) are not allowed within 30 days of Visit 2 or at any time during the study. Prescription or non-prescription cold and/or allergy medications and herbal preparations with sedative effects (such as first-generation antihistamines) or with stimulant or pressor effects (such as pseudoephedrine or ephedrine) are also prohibited. Systemic corticosteroids are prohibited; inhaled or topical corticosteroids are not prohibited. Subjects are not to use an investigational medication from another trial during the study or for the 60 days prior to study start. Prohibited concomitant medications can be resumed after Study Visit 8.

A list of concurrent medication classes that are excluded can be found in Appendix B.

6 CLINICAL EVALUATIONS

6.1 Study Procedures

A detailed schedule of events is located in Table 6.1.1.

Approximately 312 adult subjects, aged 18 to 55 years inclusive at Screening, with a diagnosis of ADHD per DSM-5™ criteria will be eligible for participation in this study. A maximum of 50 mL of blood will be drawn from subjects throughout the study duration.

Table 6.1.1 Schedule of Events

Visit Name[a]	Screen	BL	Week 1	Week 2	Week 3	Week 4	End of Study Week 5	Follow-up Phone Call Week 6	Early Termination
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Study Day Assessment	**-30 to -1**	**1**	**8 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**36 ±2d**	**7 days post V7 +2d**	
Subject consent	X								
Eligibility assessment	X	X							
Previous medications	X								
Medical history	X	X							
Demographics	X								
MINI	X								
CAADID	X								
DSM-5™ diagnosis	X								
AISRS	X	X	X	X	X	X	X		X
CGI-S	X	X	X	X	X	X	X		X
CGI-I			X	X	X	X	X		X
Height	X								
Body weight	X	X					X		X
BMI	X								
Vital signs[b]	X	X	X	X	X	X	X		X
12-lead ECG	X						X		X
Physical examination	X						X		X
Hematology	X						X		X
Serum chemistry	X						X		X

Visit Name[a]	Screen	BL	Week 1	Week 2	Week 3	Week 4	End of Study Week 5	Follow-up Phone Call Week 6	Early Termination
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Study Day Assessment	**-30 to -1**	**1**	**8 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**36 ±2d**	**7 days post V7 +2d**	
Blood alcohol	X								
HbA1c	X								
Pregnancy[c]	X	X		X		X	X		X
Urinalysis	X						X		X
CYP 2D6 testing[d]		X							
Drugs of abuse test	X	X							
C-SSRS (BL)	X								
C-SSRS (FU)		X	X	X	X	X	X		X
BRIEF-A		X					X		X
DERS		X					X		X
ASQ		X					X		X
PK Sampling						X	X		
Dispense study drug/training		X	X	X	X	X			
Drug accountability			X	X	X	X	X		X
Adverse events			X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

[a] The interval between each visit for Visits 3-6 must not exceed 9 days.

[b] At all visits, vital signs include blood pressure and pulse assessments (in triplicate via automated machine). At Screening, vital signs also include respiratory rate and temperature.

[c] Females of childbearing potential only. Serum pregnancy test will be performed at Visit 1. Urine dipstick pregnancy test is performed onsite at Visits 2, 4, 6, and 7 or early termination and may be performed at any time during study participation, if pregnancy is suspected.

[d] CYP 2D6 genetic testing for randomized subjects who opt in only. Subjects choosing to opt out are still eligible for the study.

AISRS = Adult ADHD Investigator Rating Scale; ASQ = Affective Style Questionnaire; BL = baseline; BMI = body mass index; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version; CAADID = Conners Adult ADHD Diagnostic Interview for DSM-IV; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; CYP = cytochrome P450; DERS = Difficulties in Emotion Regulation Scale; DSM-5™ = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG = electrocardiogram; FU = follow-up; HbA1c = glycosylated hemoglobin; MINI = Mini International Neuropsychiatric Interview for Adults; PK = pharmacokinetic

6.1.1 Screening Visit – Study Visit 1 (Day -30 to -1)

Before any study-specific procedures are performed, the subject must receive an explanation of all study procedures and must sign and date an Institutional Review Board (IRB)-approved written informed consent form. A subject ID number will be assigned at the Screening Visit (Visit 1), for any subject who signs an ICF.

The timing of the Screening Visit must take into account planned absences at the clinical site and the timing of the study visits according to the Schedule of Events Table 6.1.1.

The Screening Visit may be split into more than one calendar day if needed, if all required assessments are performed within 30 days of Baseline (Visit 2).

Diagnosis of ADHD based on DSM-5™ criteria and the CAADID will be confirmed for all subjects at entry by a physician or mental health profession (Master's level or higher), having at least five years of experience using ADHD rating scales for assessment of ADHD and also using the DSM for assessment of psychiatric disorders. A MINI-7.0.2 will be administered on all subjects to assist in screening for other mental health disorders that may be exclusionary.

Following confirmation of appropriate age at the Screening Visit, a diagnosis of ADHD consistent with DSM-5™ criteria will be confirmed prior to the evaluation of other inclusion and exclusion criteria.

During the Screening Period, the following activities will be performed:

- Obtain subject informed consent
- Review of inclusion/exclusion criteria
- Review of medical history
- Review of medication history (ADHD stimulant medication should be discontinued 7 days prior to the Baseline Visit)
- Demographics
- Completion of the following diagnostic criteria for ADHD performed by a physician or mental health professional (Master's Level or higher) with the required experience as outlined above:
  - CAADID
  - DSM-5™ Diagnoses
- Mini International Neuropsychiatric Interview (MINI) 7.0.2
- AISRS
- CGI-S
- C-SSRS Baseline Visit version
- Height, body weight, and body mass index (BMI)
- Blood pressure and pulse (in triplicate via automated machine), respiratory rate, and temperature
- Resting 12-lead ECG
- Physical examination
- Laboratory tests (see Appendix A)

- Serum chemistry panel (including serum pregnancy test for females of child-bearing potential)
- Hematology
- Urinalysis
- Urine drug screen for drugs of abuse testing (performed at the site)
- Blood alcohol level
- HbA1c

Blood and urine samples MUST be drawn after all other assessments are completed.

6.1.2 Baseline – Study Visit 2 (Day 1)

Once the subject is determined to be initially eligible during Screening, the Baseline (Study Visit 2, Day 1) evaluations will be completed. The timing of the Baseline Visit (Day 1) must take into account the need for study visits to occur according to the Schedule of Assessments (see Table 6.1.1).

If the subject continues to meet eligibility criteria at the Baseline Visit (Day 1), enrollment of the subject into the study will be performed by randomizing the subject through the integrated IWRS/eCRF. Double-blind study medication will be dispensed by the site pharmacy or designated, qualified study personnel (see Section 5.2).

Subjects will be instructed to start taking study medication on the morning of Day 2 with the first dose administered in the morning and the second dose four to six hours later. Subjects will be instructed to return all unused study medication with blister card at the next scheduled study visit.

The following activities will be performed pre-randomization:

- Review of inclusion/exclusion criteria
- Review of medical history
- Body weight
- Blood pressure and pulse (in triplicate via automated machine)
- C-SSRS since last visit
- AISRS
- BRIEF-A
- CGI-S
- DERS
- ASQ
- Concomitant medications assessment
- Urine pregnancy test for females of child-bearing potential
- Urine drug screen for drugs of abuse testing, performed at site
- eCRF entry for randomization

The following activities will be performed post-randomization:

- Cytochrome P450 (CYP) 2D6 genetic testing will be performed only for those randomized subjects who opt in. Subjects who opt out are still eligible for the study.

- Study drug dispensing and study medication training

6.1.3 Treatment Period – Day 2 to Day 36 (±2)

Enrolled subjects will begin taking study medication at home the morning following the Baseline Visit at 10 mg/day or placebo. From Day 2 through Day 36 (±2) inclusive, subjects will swallow study medication (2 capsules) once daily in the morning with or without food, and again four to six hours later. The dosing regimen will be twice daily for the duration of the study (4 capsules/day).

The following activities will be performed at each visit:

- Blood pressure and pulse (in triplicate via automated machine)
- AISRS
- CGI-S
- CGI-I
- Follow-up C-SSRS
- Adverse events assessment
- Concomitant medications assessment
- Pharmacokinetic sampling* (Visit 6 only)
- Urine pregnancy test for females of child-bearing potential (Visits 4 and 6 only)
- eCRF entry for study drug assignment
- Study drug accountability and study medication training
- Dispense study drug

*Blood for pharmacokinetics (Visit 6 only) MUST be drawn after efficacy and safety assessments are completed. Subjects should be instructed to record accurate dosing history (date/time) on their dosing card for the day prior to and day of their study visit.

6.1.4 End of Study – Visit 7/Day 36

The following activities will be performed during Study Visit 7 / End of Study:

- Blood pressure and pulse (in triplicate via automated machine)
- Body weight
- AISRS
- BRIEF-A
- DERS
- ASQ
- CGI-S
- CGI-I
- Follow-up C-SSRS
- Resting 12-lead ECG
- Physical Examination
- Laboratory tests
    - Pharmacokinetic sampling
    - Serum chemistry panel
    - Hematology

  - Urinalysis
  - Urine pregnancy test for females of child-bearing potential
- AE assessment
- Concomitant medications assessment
- eCRF entry for study completion
- Study drug accountability

Blood and urine samples MUST be drawn after efficacy and safety assessments are completed.

6.1.5 Early Termination

Every effort should be made to have subjects who withdraw early from the trial return to the site to complete an Early Termination Visit and return any unused study drug.

The following activities should be performed:

- Blood pressure and pulse (in triplicate via automated machine)
- Body weight
- Physical examination
- Resting 12-lead ECG
- Laboratory tests
  - Serum chemistry panel
  - Hematology
  - Urinalysis
  - Urine pregnancy test for females of child-bearing potential
- AISRS
- BRIEF-A
- DERS
- ASQ
- CGI-S
- CGI-I
- Follow-up C-SSRS
- AE assessment
- Concomitant medications assessment
- eCRF entry for early withdrawal
- Study drug accountability

6.1.6 Unscheduled Visit

Unscheduled visits are allowed if a safety concern is identified.

The following activities may be performed, including but not limited to:

- Blood pressure and pulse (in triplicate via automated machine), respiratory rate, and temperature
- Physical examination, including body weight
- Resting 12-lead ECG
- Laboratory tests (see Appendix A)

- Serum chemistry panel
- Hematology
- Urinalysis
- Urine pregnancy test for females of child-bearing potential

- Any other safety assessments per Investigator's clinical judgment
- AE assessment
- Concomitant medications assessment
- Study drug accountability and study medication training, if needed

6.1.7 Post-Withdrawal Follow-Up Telephone Call – Visit 8

The following activities will be performed during a follow-up telephone call, 7 + 2 days after Visit 7, for subjects who complete the study:

- AE assessment
- Concomitant medications assessment

6.2 Description of Assessments

Safety and efficacy evaluations will be performed during the study. The schedule of these procedures is described in Table 6.1.1**.**

6.2.1 Baseline Characteristics

6.2.1.1 Demography

Information relating to the subject's gender, age, race, and weight/height will be collected at screening and recorded on the appropriate eCRF page.

6.2.2 Medical History

The medical history of each subject will be collected and recorded on the appropriate eCRF page. This history will also include any abnormalities found during the physical examination conducted at the Screening Visit. History of prior and concomitant medications will be recorded as indicated in Section 5.9.

6.2.3 Efficacy Parameters

As much as possible, the same individual should perform a given efficacy assessment at every visit when the assessment is required. Efficacy will be assessed by the following measures collected during the study:

6.2.3.1 Primary Efficacy Variable

The primary efficacy endpoint is the change in AISRS total score from Visit 2 (Baseline) to Visit 7 (End of Study) in AR19 treated subjects compared to placebo.

6.2.3.2 Secondary Efficacy Variables

- CGI-S at Visit 7 compared to Baseline
- CGI-I at Visit 7
- Changes from Baseline of AISRS subscale scores compared to Visit 7
- Changes from Baseline of the BRIEF-A, subscales, indices, and composites compared to Visit 7

6.2.3.3 Exploratory Endpoints

Items pertaining to emotional dysregulation are contained in certain domains of several existing tools, including the BRIEF-A, DERS, and ASQ, which will be used in this study.

Exposure-response relationships using population pharmacokinetics will be explored. A nonlinear mixed-effect modeling approach will be used for population pharmacokinetic analysis. To aid the population pharmacokinetic analysis, two blood plasma samples will be collected from all subjects. **Error! Reference source not found.** provides instructions on processing and shipment of samples to the central laboratory. The samples collected will include pre-dose up to approximately 6 hours following drug administration on planned subject visit days (Visit 6 and Visit 7). Subjects should be instructed to record accurate dosing history (date/time) on their dosing card for the day prior to and day of their study visit. Additional AR19 concentration vs time data may be pooled from other studies and included in population pharmacokinetic analysis. Covariates such as age, weight, liver function (AST and ALT), CYP 2D6 metabolizer status, and race and their effect on AR19 pharmacokinetic parameters will be explored. The developed population pharmacokinetic model will be used to conduct exposure-response analysis.

6.3 Assessments

6.3.1 Adult ADHD Investigator Rating Scale (AISRS)

The AISRS is a validated 18-item scale that corresponds directly to the 18 ADHD items in the Diagnostic and Statistical Manual of Mental Disorders.[25] It includes adult prompts for each item. The AISRS will be used to determine trial eligibility. An AISRS assessment will be completed at Study Visits 1 through 7. The Investigator or other designated, qualified individual from the study research team will complete the assessment.

6.3.2 Clinical Global Impression Scales (CGI)

The Clinical Global Impression Scales are used to measure features associated with ADHD. A global assessment of disease severity (CGI-S) will be completed at Study Visits 1 through 7. A global assessment of disease improvement (CGI-I) relative to baseline will be completed at Study Visits 3 through 7. The Investigator or designated, qualified individual from the study site will perform the assessment.

6.3.3 Mini International Neuropsychiatric Interview 7.0.2 (MINI)

The MINI is a short, structured diagnostic interview developed for DSM-5™. It assesses the 15 most common psychiatric diagnoses and can be completed in about 15 minutes.[26] The MINI will be completed at Screening.

6.3.4 Conners' Adult ADHD Diagnostic Interview for DSM-IV™ (CAADID)

The CAADID is a structured interview that assesses childhood and adult ADHD symptoms. Although the version used was designed for DSM-IV™, it can be adapted to make an ADHD diagnosis using DSM-5™ criteria.

6.3.5 Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A)

The BRIEF-A is a standardized measure designed to assess adult executive functioning and self-regulation.[7] It is composed of 75 items and 9 clinical scales which include: Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organization of Materials. The clinical scales compose two indexes: Behavioral Regulation (BRI) and Metacognition (MI), and these indexes form the overall summary score, the Global Executive Composite (GEC).

6.3.6 Difficulties in Emotional Regulation Scale (DERS)

The DERS is a validated non-disease state scale consisting of 39 items. These items are grouped to reflect difficulties in: a) awareness and understanding of emotions; b) acceptance of emotions; c) ability to engage in goal directed behavior and refrain from impulsive behavior while experiencing negative emotions; and d) access to emotional regulation strategies perceived as effective.[8]

6.3.7 Affective Style Questionnaire (ASQ)

The ASQ is a 20-item questionnaire used to measure individual styles in emotional regulation. The styles assessed in this instrument are: a) suppression and other strategies to conceal or avoid emotion; b) more able to access emotional information in adaptive problem solving (i.e., to be better able to modulate emotional experience and expression according to contextual demands); and c) reflecting comfort and non-defensiveness in response to arousing emotional responses, thus tolerating the aroused emotional response.[9]

6.4 Safety Parameters/Assessments

All subjects who enter the study will be assessed for safety. Safety will be monitored by AEs assessed at each post-dose visit. In addition, the C-SSRS will be administered at Screening and all subsequent scheduled visits to assess emergent suicidal thoughts or behaviors. Medical history will capture all medical conditions at Visits 1 (Screening) and 2 (Baseline). Physical examinations and clinical laboratory tests will be conducted at Visit 1 (Screening) and Visit 7 (End of Study), and at an Early Termination Visit, if necessary and can be conducted at any post-dose visit, if the Principal Investigator deems it necessary.

The following will be assessed throughout the study according to the Schedule of Events Table 6.1.1:

- Incidence and severity of AEs (see Section 7).
- Incidence of clinically significant changes from Baseline in the C-SSRS.

6.4.1 Physical Examination

A full physical examination will be performed at Visits 1 (Screening), 7 (End of Study), and at an Early Termination Visit, if necessary. This will include physical examination of the following body areas and systems: head and neck, abdominal, chest, cardiovascular, heart, respiratory, musculoskeletal, skin, neurological, and endocrine. This assessment is optional at unscheduled visits, per the Investigator's discretion.

Body weight will also be measured at Screening (Visit 1), Baseline (Visit 2), and at the End of Study (Visit 7) or at the Early Termination Visit, if necessary.

6.4.2 Vital Signs

Blood pressure and pulse will be assessed at all study visits and will be taken using automated machines programmed to take 3 consecutive readings (at least 2 minutes apart). Subjects should be comfortably seated for at least a few minutes prior to blood pressure readings. Respiratory rate, height for BMI, and temperature will be measured at Screening (Visit 1) only.

6.4.3 Electrocardiography

A 12-lead ECG will be recorded at Screening (Visit 1), End of Study (Visit 7) and at an Early Termination Visit (if necessary) by the Investigator or other designated, qualified individual from the study site. The ECGs will be assessed by a central reader(s). ECGs can be performed at unscheduled visits, per the Investigator's discretion.

6.4.4 Hematology, Serum Chemistry and Urinalysis

At Screening (Visit 1), End of Study (Visit 7) and at an Early Termination Visit (if necessary), laboratory tests will include a non-fasting serum chemistry panel, hematology (complete blood count), and urinalysis. Laboratory assessments are optional at Unscheduled Visits. For a complete list of laboratory tests, please see Appendix A.

CYP 2D6 genetic testing will be performed only at Baseline (Visit 2) for those randomized subjects who opt in. Subjects who opt out are still eligible for the study. **During the trial, CYP 2D6 testing results will be blinded to the subject and investigative site in order to ensure protocol efficacy and safety assessments remain unbiased.**

Detailed sample collection, handling, processing, and shipment instructions will be provided by Sponsor's laboratory designee prior to the start of the study.

6.4.5 Pregnancy Test and Contraceptives for Females of Child-Bearing Potential

At the Screening Visit (Visit 1), a serum pregnancy test will be performed for all female subjects of child-bearing potential.

Urine dipstick pregnancy tests will be performed onsite at Visit 2 (Baseline) and Visits 4, 6, and 7 (End of Study) or early termination visit (if necessary) and may be performed at any time during study participation, if pregnancy is suspected. If positive, confirmation should be performed via a serum pregnancy test.

Moreover, females of child bearing potential must agree to use adequate birth control methods to prevent pregnancy throughout the study. Examples of medically highly effective forms of birth control include:

- Surgical sterility (via vasectomy, hysterectomy, or bilateral ligation) or post-menopausal females
- Sexual partner is sterile, or of the same sex
- Implants of levonorgestrel in females
- Oral contraceptive (combined or progesterone only) in females
- Double-barrier method (any combination of physical and chemical methods)
- Intrauterine device in females, or other method with published data showing that the lowest expected failure rate is less than 1% per year
- Complete abstinence from penile-vaginal intercourse

6.4.6 Drugs of Abuse Testing

A urine test for drugs of abuse will be performed at the site during Visit 1 (Screening) and Visit 2 (Baseline). The following drugs will be included: amphetamine, barbituates, benzodiazepenes, cocaine, opiates, methadone, methamphetamine, and phencyclidine (PCP).

6.4.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a brief, Investigator-administered questionnaire that provides for the identification, quantification, and standardized assessment of the occurrences and severity of suicidal ideation and behavior.[28]

The Baseline version of the C-SSRS will be administered to all subjects at the Screening Visit. The “Since Last Visit” version will be used at all subsequent study visits (and Early Termination, if necessary). The Investigator or other designated, qualified individual at the clinical site will perform these assessments.

7 ADVERSE EVENTS

7.1 Definition of an Adverse Event

An AE is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.” An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

Adverse events will be identified at the times indicated in the schedule by asking the subject a neutral question such as: "How have you been feeling since your last visit?" Adverse events may also be reported spontaneously at any time. Any adverse or unexpected events, signs, or symptoms will be fully recorded on the AE form in the eCRF including details of onset, resolution, frequency, severity (as defined below), seriousness, relationship to the drug, effect on the study drug, treatments administered, and outcome. Any AE that occurs during the study will be followed, whenever possible, until it returns to the baseline condition or becomes stable with no further change expected.

Beginning with the first dose of study drug on Day 2, all AEs occurring up to study completion, must be recorded in the eCRF. All changes in health occurring prior to study drug dosing should be recorded as medical history.

7.2 Definition of a Serious Adverse Event (SAE)

An SAE is any event or reaction that fulfills one or more of the following outcomes:

- Results in death
- Is life threatening. This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital defect or birth defect
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

All SAEs must be recorded on the eCRF adverse event form as “serious” and submitted promptly during the study. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject’s stable or chronic condition or intercurrent illness.

Reports for hospitalization for elective procedures do not need to be reported as SAEs, if there are no precipitating signs/symptoms or worsening of a pre-existing condition that necessitated the procedure. However, SAEs must be reported for any complications resulting from a procedure that prolonged the hospitalization.

Serious adverse events should be reported as outlined in Section 7.5.

7.3 Collection of Adverse Events

The collection of AE information will start with the first dose of study drug (Day 2) and continue through the post-withdrawal follow-up phone call (i.e., 7 days after Visit 7). The collection of SAE information will start with the first dose of study drug (Day 2) and continue 30 days after the subject's last dose of study drug. For subjects who terminate early, all AEs and SAEs should be treated as medically appropriate. Should a subject have an ongoing SAE at the last study contact or has an SAE within 30 days after Visit 7, the subject will continue to be followed as specified in Section 7.8.

To detect the occurrence of AEs and SAEs, the physician should use non-direct neutral questioning of the subject at each post-dose clinical visit. Information of AEs and SAEs may also be given voluntarily by the subject at any time during the study.

7.4 Assessment of Adverse Events

The Investigator will assess each AE according to severity and relatedness to study drug.

7.4.1 Assessment of Adverse Event Severity

The following guidelines for rating severity of AEs should be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study medication.

Moderate: Discomfort enough to cause interference with usual activities; the study medication may have been interrupted.

Severe: Incapacitating with inability to do work or do usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may have been stopped, and treatment for the event may be required.

The term "severe" is often used to describe the intensity of a specific event, as in mild, moderate, or severe myocardial infarction; the event itself, however, may be of relatively minor medical significance, such as severe headache. This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The Investigator must decide whether each AE meets the definition of an SAE.

7.4.2 Assessment of Adverse Event Relatedness

The relatedness of an AE to study medication will be determined by the Investigator using the following definitions:

Related: The AE is clearly related to the study drug. This assessment means there is evidence to suggest a clear, causal relationship between the study drug and the AE.

Possibly Related: The AE may be related to study drug. A "possibly" assessment suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.

Unlikely Related: The AE is doubtfully related to study drug. An "unlikely" assessment suggests other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear more likely to explain the reported AE.

Not Related: The AE is clearly not related to the study drug.

7.4.3 Recording of AEs and SAEs

All AEs occurring during this clinical study will be recorded in the eCRF in precise medical terms, along with the date of onset and the date of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should group signs and symptoms together into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to the study medication. The severity of the AE and its relationship to the study medication will be assessed by the Investigator.

The action taken and the outcome must also be recorded. The possible actions concerning study medication are:

- Drug withdrawn
- Dose not changed
- Unknown
- Not applicable
- Dose interrupted

Recorded outcomes include:

- Recovered/Resolved
- Recovering/Resolving
- Not recovered/Not resolved
- Resolved with sequelae
- Fatal
- Unknown

7.5 Reporting of Serious Adverse Events

7.5.1 Serious Adverse Event Notification

Serious adverse events must be reported within 24 hours of knowledge of the occurrence. This includes events that occur following completion of treatment with study drug. Additionally, if an Investigator learns of any SAEs that occurred after study completion for which there is a reasonable possibility of study drug relationship, that event should be reported to the Sponsor within 24 hours.

The eCRF SAE Reporting Form will be completed with as much information as is available and must include information below within 24 hours of when the investigative site becomes aware of the event.

Required SAE information:

- Name of Reporter/Investigator
- Subject identification
- Adverse event term
- Date of onset
- Criteria of seriousness
- Study drug relationship

For assistance regarding SAE reporting, please contact the [redacted]

7.5.2 SAE Expedited Reporting

For each SAE, the Investigator should assess whether there is a reasonable possibility that the event may have been caused by the study drug ("drug related") using the categories given in Section 7.4.2. The Sponsor or designee will notify all Investigators of an SAE. Those SAEs that meet reporting criteria will be submitted to the appropriate Regulatory Authorities as required by clinical trial regulations. The Investigator is responsible for notifying his/her respective IRB.

7.6 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study, the event must be reported to [redacted] upon receipt of information by the study staff. While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Pregnancy must be reported within 24 hours from first knowledge on the pregnancy eCRF. Any pregnancy will be followed through delivery for the observation of any SAEs including congenital abnormalities. Fatalities and spontaneous abortions must be reported as SAEs.

7.7 Emergency Unblinding

Unblinding should occur only when knowing the treatment assignment has a bearing on the medical treatment or evaluation of a subject. Whenever possible, the need to unblind should be discussed with the Medical Monitor prior to unblinding. In the event of an emergency, the Investigator, Pharmacist, or designated qualified individual may obtain the subject's blinded treatment via IWRS. If an individual designated to perform emergency unblinding does not have access to the IWRS, Sponsor Designee may be contacted and can perform the unblinding for that individual. A subsequent written report, including all pertinent details, must be submitted to the Medical Monitor within 24 hours of the unblinding. Whenever possible, the blind of the subject should be maintained.

7.8 Follow-up of AEs and SAEs

All AEs must be followed until they resolve (return to normal or baseline values), stabilize, or are judged by the Investigator to be no longer clinically significant. Serious adverse events observed during the study should be followed by the responsible Investigator at the clinical site until they resolve or stabilize, the subject is lost to follow-up, or the events are otherwise explained.

8 STUDY ADMINISTRATION

8.1 Quality Assurance/Quality Control

8.1.1 Direct Access to Source/Data Documents

The Investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data and documents.

8.1.2 Periodic Monitoring

The Sponsor or its designee will monitor all aspects of the study with respect to current Good Clinical Practice (GCP) and standard operating procedures for compliance with applicable regulations. These individuals must have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

Monitoring of the study progress and conduct will be ongoing. The Sponsor or its designee will be responsible for the following:

- Monitoring study conduct to ensure that the rights of subjects are protected
- Monitoring study conduct to ensure study compliance with GCP guidelines
- Monitoring accuracy, completion, and verification of source documents for study data.

8.1.3 Audit and Inspection

All data recorded during the study will be made available by the site for audit against source data and for compliance with GCP and specific protocol requirements.

8.1.4 Confidentiality of Subject Data

All information obtained during the conduct of the study that relates to an individual subject will be regarded as confidential. Throughout the study, participating subjects will be referenced using their allotted subject ID and initials. They will not be referred to by name in any document concerning the study or disclosed to any person not under the direct control of the Investigator.

8.2 Data Handling and Record Keeping

8.2.1 Electronic Case Report Forms (eCRFs)

Adequate and accurate case records will be maintained and all relevant observations and data related to the study will be recorded. This will include (but will not be limited to) medical history/physical examination, vital signs, medication history, pregnancy tests, a check of inclusion and exclusion criteria, drug administration, a record of sample collection, AEs, and final evaluation.

The eCRFs will be signed electronically by the Principal Investigator after the review (date and time will be captured in the eCRF audit trail). After the completion of the study, completed eCRFs will be electronically transferred to the Sponsor and/or designee and stored in the archives according to the Data Management Plan for the study.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once eCRFs are signed by the Investigator, the data manager will lock the eCRFs for data analysis.

8.2.2 Study Records Retention

All primary data that are a result of the original observations and activities of the study that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period of at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified.

The Investigator must maintain adequate records for the study including completed CRFs, medical records, laboratory reports, signed ICFs, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with the IRB and the sponsor, and other pertinent data.

The Investigator will notify Arbor in writing of the relocation of any study records away from the clinical site after study closure. The Investigator must contact Arbor in writing prior to the destruction of any study records, or in the event of loss of any study records.

8.3 Termination of the Study

The Sponsor reserves the right to terminate the study in the interest of subject welfare.

9 STATISTICAL ANALYSES

9.1 Determination of Sample Size

The primary efficacy endpoint is change from Baseline in AISRS total score at Visit 7 (Week 5). A Bonferroni adjustment will be utilized for the primary efficacy analysis where each AR19 dose will be tested against placebo separately using an alpha of 0.025 for each test.

Eighty-seven (87) subjects per treatment group will provide approximately 90% power to detect a 7.0-point difference in mean change from Baseline to Visit 7 in the AISRS total score between one of the AR19 doses and placebo with a standard deviation of 13.0 and Type I error of 0.025 using a two-sample test. To account for an approximate 20% dropout rate, a total of 104 subjects will be randomized to each of the three treatment groups for a total of 312 randomized subjects.

9.2 General Methodology

All continuous study assessments will be summarized by treatment and time point using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point using frequency counts and percentages. Hypothesis testing, unless otherwise indicated, will be two-sided and performed at the 5% significance level.

A detailed statistical analysis plan (SAP) will be written and finalized prior to database unblinding.

9.3 Subject Populations for Statistical Analysis

The three analysis populations for this study are defined below. Identification of the subjects to be included in each analysis population will be determined prior to database unblinding.

9.3.1 Safety Population

All patients who are randomized and receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety assessments. Results will be presented “as treated.”

9.3.2 Full Analysis Set (FAS) Population

All patients who are randomized, receive at least one dose of study medication, and had one or more post-Baseline on-treatment primary efficacy assessment(s) will be included in the FAS Population. The FAS Population is the primary analysis population for clinical efficacy. Results will be presented “as randomized.”

9.3.3 Per Protocol Population

All patients who are in the FAS population and who do not have any major protocol deviations will be included in the PP Population. The PP Population will be used as a sensitivity analysis for clinical efficacy.

9.4 Primary Efficacy Analysis

The primary efficacy analysis will be performed on the FAS population.

For the primary efficacy endpoint, change from baseline in AISRS at Visit 7 (Week 5), the two AR19 dose levels (20 and 40 mg/day) will be compared with placebo. To account for these comparisons, a Bonferroni multiple comparison adjustment will be utilized. Both comparisons will be conducted at the 0.025 (0.05/2) alpha level. No other adjustments for multiplicity will be applied to any other endpoints or comparisons.

Change from Baseline in AISRS at Visit 7 will be compared between each of the two different AR19 dose groups and the placebo group using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). This model will include fixed effects for treatment, week, baseline AISRS, and the treatment-by-week interaction. Study week will be included in the model as a categorical variable. Within this model, pairwise comparisons (using least squares [LS] mean contrasts) will be made to compare AISRS at Visit 7 for each AR19 dose level with placebo separately (primary efficacy outcome). Treatments will also be compared at other weeks as secondary analyses. If differences between baseline characteristics exist between the three treatment groups in this comparison, it will be investigated whether adjustment for these characteristics is clinically relevant and necessary as a sensitivity analysis.

All available data will be used; there will be no imputation of missing data.

9.5 Secondary Efficacy Analyses

The primary analysis will be repeated on the PP population using the MMRM analysis described in Section 9.4.

The secondary efficacy outcomes include:

- AISRS hyperactivity/impulsivity subscale scores
- CGI-S
- CGI-I
- BRIEF-A

For the AISRS, the proportion of responders (defined as a subject who has a change from Baseline of 30% or greater in the AISRS) will also be presented.

The number and percentage of subjects who have each category of the CGI-S and CGI-I at each time point will be presented by treatment group. Cochran-Mantel-Haenszel row mean score tests will be used to compare the treatment groups. CGI-S and CGI-I results will also be summarized treating the responses as continuous values. A MMRM will be utilized to

compare treatments at each time point. The model will include fixed effects for treatment, week, and the treatment-by-week interaction.

BRIEF-A will be summarized descriptively over time utilizing observed and change from Baseline scores. Treatments will be compared at each time point utilizing MMRM models on change from Baseline scores. The model will include fixed effects for treatment, week, baseline value, and the treatment-by-week interaction.

9.6 Exploratory Endpoints

Similar to the BRIEF-A, DERS and ASQ scale scores will be summarized descriptively over time utilizing observed and change from Baseline scores. Treatments will be compared at each time point utilizing MMRM models on change from Baseline scores. The model will include fixed effects for treatment, week, baseline value, and the treatment-by-week interaction.

The pharmacokinetic analysis and reporting will be covered in a separate SAP and report.

9.7 Handling of Drop-Outs or Missing Data

For subjects who discontinue prematurely, a MMRM approach will be used to address missing data. Other imputation methods (e.g., last observation carried forward [LOCF] or multiple imputation) may be used as sensitivity analyses. Full details will be described in the SAP.

9.8 Safety Analyses

All safety data will be analyzed descriptively by treatment group using the Safety Population.

9.8.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent AEs will be defined as any event with a start date occurring on or after first dose of study medication.

The incidence of treatment-emergent AEs will be summarized by body system, preferred term, and treatment group. If a subject reports the same AE more than once, then that subject will be counted only once for the summary of that AE, using the most severe intensity or highest relationship to study medication.

Treatment-emergent AEs will be summarized as follows:

- All treatment-emergent AEs;
- All treatment-emergent AEs by intensity;
- All treatment-emergent AEs by relationship to study drug;
- All treatment-emergent SAEs; and
- All treatment-emergent AEs that led to premature discontinuation from study.

9.8.2 Clinical Laboratory Assessments

Hematology, blood chemistry, and urinalysis parameters will be summarized at Baseline and at Visit 7, as well as changes from Baseline to Visit 7. Laboratory values and changes from Baseline in laboratory values will be summarized descriptively overall and by treatment group.

A summary of shifts from Baseline to final evaluation will be provided for each treatment group for each parameter. The normal range for each parameter will be used to create categories of low, normal, or high. Any result higher than the ULN or lower than the LLN will be categorized as high or low respectively, and any result within the lower and upper limits of normal will be categorized as normal. The number and percentage of subjects in each treatment group in each shift category from Baseline to final evaluation will be shown for each parameter.

9.8.3 Vital Signs and ECGs

Vital sign measurements will be summarized at Baseline and at each study visit. In addition, changes from Baseline to each study visit in vital sign and ECG measurements will be summarized.

ECG measurements will be summarized at Baseline and at Visit 7. In addition, changes from Baseline to Visit 7 in vital sign and ECG measurements will be summarized.

The incidence of sponsor-defined, potentially clinically significant, post-treatment vital sign values will also be presented by treatment group.

9.8.4 Other Safety Variables

Concomitant medications taken during study will be categorized by World Health Organization (WHO) classification for therapeutic class and drug name and summarized by number and percentage of subjects by treatment group. Prior medications will also be summarized.

C-SSRS data will be listed.

10 ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1 Institutional Review Board

The Principal Investigator will provide the IRB with all requisite materials, including a copy of the protocol, ICF, and any subject information or advertising materials. The study will not be initiated until the IRB provides written approval of the protocol and the ICF and until approved documents have been obtained by the Principal Investigator and copies received by the Sponsor's designee. All amendments will be sent to the IRB for information (minor amendment) or for submission (major amendment) before implementation. The Principal Investigator will supply the IRB and the Sponsor's designee with appropriate reports on the progress of this study, including any necessary safety updates, in accordance

with the applicable government regulations and in agreement with policies established by the Sponsor.

10.2 Ethical Conduct of the Study

The study will be performed in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations, FDA GCP Regulations (21 Code of Federal Regulations parts 50, 56, and 312) and International Conference on Harmonisation (ICH) guidelines for GCP (E6) and clinical safety data management (E2A).

10.3 Subject Information and Informed Consent

In compliance with GCP guidelines, all subjects will be informed of the purpose of the research, possible risks of participation, and their rights to withdraw at any time from the study without prejudice and without jeopardy to the subject's future medical care at the center. Each subject must give informed written acknowledgment (signed ICF) to the Investigator prior to participation in the study. Each subject residing in the US must also provide HIPAA authorization. Each subject will be given a copy of their signed ICF.

No subject is to participate in study activities until written informed consent has been obtained. Documentation of the informed consent process and subject information discussion must appear in the subject's medical record, and include a statement that informed consent was obtained prior to participation in the study. Signed ICF acknowledgments must remain in the subject's file and be available for verification by monitors, auditors, and/or inspectors at any time.

11 APPENDICES

11.1 Appendix A

Listing of Laboratory Assays

Serum chemistry panel:	**Hematology complete blood count:**
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate Bilirubin (total) Blood urea nitrogen (BUN) Calcium Chloride Creatinine Glucose (non-fasting) Potassium Sodium Total protein Uric acid	White blood cell count (WBC) Red blood cell count (RBC) Hemoglobin Hematocrit (packed cell volume) Mean cell volume (MCV) Mean cell hemoglobin (MCH) Mean cell hemoglobin concentration (MCHC) Platelet count Differential WBC
Other:	
Thyroid-stimulating hormone (TSH) Serum pregnancy test (females of child-bearing potential) Urine dipstick pregnancy test (onsite) Drugs of abuse screen (urine onsite) Blood alcohol level Glycosylated hemoglobin (HgA1C) Hepatitis C virus RNA (for subjects who report positive history of HCV infection that is now completely treated) CYP 2D6 (only samples from randomized subjects who opt in will be analyzed) Population pharmacokinetic samples	

11.2 Appendix B

Prohibited Concomitant Medications

Subjects are not to use an investigational medication from another trial during the study or for the 60 days prior to study start. Prohibited concomitant medications can be resumed after Visit 8.

Sedative hypnotics are excluded unless they have been on a stable dose at least one month prior to screening and will be continuing their use during the study.

The table below shows examples of prohibited concomitant medication classes that are not allowed in the study; the list is not intended to be comprehensive. Some of the example medications listed are included more than once.

Prohibited Medication Class	**Examples**
Any stimulant used for any indication or non-stimulant medications for ADHD	Stimulants: methylphenidate, dexmethylphenidate, amphetamine, dextroamphetamine, lisdexamfetamine Non-stimulants: amoxetine, guanfacine, clonidine, bupropion
Monoamine oxidase inhibitors	selegiline, isocarboxazid, phenelzine, tranylcypromine
Serotonergic drugs	SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's wort
Mood stabilizers	lithium, valproate, quetiapine
Anticonvulsants	phenobarbital, phenytoin, primidone
Anticoagulants	warfarin
Antipsychotics	risperidone, olanzapine, haloperidol
Tricyclic antidepressants	desipramine, protriptyline
Medications with pressor effects	phenylephrine, pseudoephedrine, ephedrine, midodrine, fludrocortisone
Systemic corticosteroids	prednisone, methylprednisolone, dexamethasone

Psychotropic medications or those with psychotropic properties (some are already noted above)	Antidepressants, antipsychotics, mood stabilizers, antianxiety agents, certain non-prescription cold allergy medications (e.g., diphenhydramine, dextromethorphan)
Acidifying agents	Gastrointestinal acidifying agents (e.g., glutamic acid HCl, ascorbic acid) Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts)
Alkalinizing agents	Gastrointestinal alkalinizing agents (e.g., sodium bicarbonate) Urinary alkalinizing agents (e.g., acetazolamide)
CYP 2D6 inhibitors	paroxetine, fluoxetine, quinidine, ritonavir
Other medications	halogenated anesthetics, phenylbutazone, chlorpromazine, ethosuximide

ADHD = attention deficit hyperactivity disorder; CYP = cytochrome P450; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

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