STATISTICAL ANALYSIS PLAN

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

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LIST OF ABBREVIATIONS

Commonly used abbreviations (such as units and abbreviations used for electrocardiogram assessments) are not included in this list.

ADHD	Attention Deficit Hyperactivity Disorder
AISRS	Adult ADHD Investigator Rating Scale
AE(s)	Adverse event(s)
ASQ	Affective Style Questionnaire
ATC	Anatomical Therapeutic Chemical
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Version
CAADID	Conners' Adult ADHD Diagnostic Interview for DSM-IV™
CBC	Complete Blood Count
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DERS	Difficulties in Emotional Regulation Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Ed.
ECG	Electrocardiogram
FAS	Full Analysis Set
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IR	Immediate Release
IWRS	Interactive Web Response System
LS Mean	Least-Squares Mean
MINI	Mini International Neuropsychiatric Interview for Adults
MMRM	Mixed Model for Repeated Measures
PFC	Prefrontal Cortex
PP	Per Protocol
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SE	Standard Error

1. PURPOSE OF THE STATISTICAL ANALYSES

The purpose of the analyses described in this document is to compare the safety and effectiveness of AR19 (Amphetamine Sulfate) compared to placebo in adult subjects with Attention Deficit Hyperactivity Disorder (ADHD).

The statistical analysis plan (SAP) is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials [1] and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports [2].

2. PROTOCOL SUMMARY

2.1 Introduction

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. 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%. 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.

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. 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. 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).

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

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.

[redacted] is a marketed immediate-release (IR) formulation of amphetamine sulfate indicated for narcolepsy, ADHD, and exogenous obesity. 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. Enhancements to the current IR formulation of [redacted] 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.

Results of a recent PK study verified that AR19 is bioequivalent to currently marketed [redacted].

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

2.2 Study Objectives

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

2.3 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 Events (Appendix 14.1).

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.

2.4 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.

2.5 Method of Assigning Subjects to Treatment

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.

Randomization will occur via Interactive Web Response System (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.

2.6 Treatment Regimens

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 2.6.1 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 2.6.2 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.

2.7 Sample Size Determination

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.

3. GENERAL ANALYSIS, REPORTING, AND PROGRAMMING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be given in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

Descriptive statistics for continuous parameters will include number of observations (n), mean, median, standard deviation, minimum, and maximum values. Descriptive statistics for categorical parameters will include frequency counts and percentages. All study data will be listed by subject, treatment group, sequence (as applicable), and time point (as applicable).

Hypothesis testing, unless otherwise indicated, will be two-sided and performed at the 2.5% significance level. When confidence intervals are presented, they will be two-sided with a confidence coefficient of 97.5%. P-values will be reported to 3 decimal places if greater than 0.001. If less than 0.001, report '<0.001'. P-values and significant levels will be reported as 0.025 rather than .025.

Data will be summarized based on the recorded visit; no visit windowing will be performed.

No preliminary rounding will be performed; rounding will only occur after analysis. To round, the digit to right of last significant digit will be considered: if < 5 then round down, if ≥ 5 then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. Minimums and maximums will be presented with the same precision as the original data.

All analyses will be performed using the SAS System® version 9.3 or higher.

The following general programming conventions will apply:

Exposure Days: (Last dosing date – first dosing date + 1)

Compliance: [(Number of doses taken)/(number of doses planned)]*100

Duration days: (End/resolution date – start/onset date +1)

Study day: (Date of interest – first dosing date +1) if date of interest is on or after the first dosing date: (Date of interest – first dosing date) if date of interest is before the first dosing date.

4. ANALYSIS POPULATIONS

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. The database will be locked and unblinded after the SAP is signed and authorized, there are no outstanding data issues, and the final analysis populations are imported into the study database.

4.1.1 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.”

4.1.2 Full Analysis Set (FAS) Population

All subjects 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.”

4.1.3 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.

4.2 Disposition of Subjects

Subject accountability will be summarized based on all subjects enrolled into the study by treatment sequence. The following patient accountability information will be presented:

- The number and percentage of subjects who enrolled in the study, who were randomized, who completed the study, and who prematurely discontinued from the study
- The number and percentage of subjects who discontinued prematurely, by reason for premature discontinuation
- The number and percentage of subjects in the Safety, FAS, and PP populations

In addition to these summaries, a listing by patient will be provided that shows treatment, subject number, sex, age, race, reason for discontinuation, and any specific comments related to discontinuation.

4.3 Protocol Deviations

Protocol deviations will be jointly assessed by the sponsor and Rho and summarized by treatment sequence and overall. The final protocol deviation listing for the study (prior to unblinding) will be approved by the sponsor.

Protocol deviations will be categorized into, but not limited to, the following protocol deviation categories and will be classified as major or minor:

- Prohibited Medication/Therapy
- Dosing or Randomization Error
- ICF/Consent Process
- Eligibility Criteria Not Met
- Missed Study Procedure: Efficacy or Safety Assessment
- Unreported AEs/SAEs
- Other Protocol Deviation (not otherwise defined)

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics including age, sex, race, weight and height will be summarized by treatment sequence and overall on the safety, FAS, and PP populations.

5.2 Prior and Concomitant Medications

Prior medications are medications that were taken prior to the first dose of study medication. Concomitant medications are medications that were taken during the treatment period.

Medications with partial start dates will be determined as concomitant medications by using available non-missing information. Completely missing start dates (i.e. missing information for medication start day, month, and year) are assumed to be concomitant medications.

Missing end dates for prior and concomitant medication will be imputed based on the following rules:

- If only the year is known, the date will be set to 31 December of that year. If the year is the same as the treatment start date, the date will be set to the treatment end date.

- If the year and month are known the date will be set to the end of the specified month.

- If the end date is completely missing it will be assumed that the medication is ongoing for the duration of the study, and as such regarded as concomitant.

- If these rules are followed and the completed end date is after the last visit date, the end date will be set to the last visit date.

The frequency of subjects using prior and concomitant medications at any stage of the study will be summarized according to WHO-DD Version 2018.01 Anatomical Therapeutic Chemical (ATC) level 2 and level 4, by treatment on the Safety Population. The ATC levels will be presented in decreasing order of the total number of subjects (frequency) who used each medication. The ATC levels with the same frequency will be presented alphabetically.

5.3 Medical History

Medical history findings will be coded using MedDRA 21.0 and will be summarized descriptively by treatment on the Safety Population.

6. MEASUREMENT OF TREATMENT COMPLIANCE

Compliance rates will be calculated by dividing the number of doses taken by the number of doses that should have been taken during the treatment period and will be summarized by treatment group.

Compliance will be further categorized and summarized by treatment group as follows:

- <80%.
- 80% to 100%.
- >100%.

7. EFFICACY EVALUATION

7.1 Overview of Efficacy Analysis Issues

7.1.1 Handling of Dropouts or Missing Data

Missing data could occur under either or both of the following scenarios: (1) missing or invalid data for individual questions in the AISRS; and (2) missing AISRS total scores at individual visits. The approach to handling missing data under these scenarios is described below.

7.1.1.1 Missing Individual Items in the AISRS Scale

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. 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.

Missing or invalid data for individual questions will be handled by rules specified as follows:

- If 4 or more individual items in the AISRS have missing or invalid data, the AISRS total score will be set to missing.

- If 3 or less individual items in the AISRS are missing or invalid, the values for the missing individual items will be imputed using the mean of the non-missing individual items for the particular subject at that visit, rounded up to the nearest integer.

- If any item within an AISRS subscale is missing or invalid, the entire subscale score will be set to missing.

7.1.1.2 Missing AISRS Total Scores at Individual Study Visits

Primary Analysis

No imputation of missing AISRS total scores at individual visits will be done for the primary efficacy analysis. The mixed model repeated measures methods used to analyze the primary endpoint has been designed to utilize all available data and provides valid estimates under the assumption of data which are missing completely at random or missing at random. Accordingly, all subjects with one dose of study medication and at least one post-baseline on-treatment assessment of the primary efficacy variable will be included in the model.

Sensitivity Analyses

To explore the sensitivity of the primary analysis results, analyses using two imputation methods may be performed: a placebo-based multiple imputation (MI) pattern-mixture model (PMM) analysis and a tipping point analysis using the PMM. If the dropout rate in this study is <2%, these sensitivity analyses will not be performed. This decision will be made prior to database unblinding.

Sensitivity analysis one: Placebo-based MI PMM

To explore the robustness of the primary analysis results, a sensitivity analysis will be carried out that assesses the situation where the data are not missing at random (NMAR). More specifically, all subjects taking AR19 who discontinue for any reason will be assumed to behave like placebo subjects.

A controlled, multiple imputation approach based on PMM will be applied for those subjects on AR19 using the 'Copy Reference' approach [3]. More specifically, missing data for those subjects taking AR19 who discontinued early will be imputed based on the posterior distribution of the placebo group. Missing data for placebo subjects who discontinue early will also be imputed using the observed

values of the placebo group.

Data will be imputed using SAS PROC MI (v9.3 or later) using the full conditional specification method (FCS). Twenty burn-in iterations will be performed prior to each imputation. The imputation model will include observed non-missing AISRS scores, baseline AISRS score, age, and sex. One hundred imputed datasets will be generated for analysis.

The same model used in the primary analyses will be fit to each of the 100 datasets. The parameter estimates and standard errors will be combined using PROC MIANALYZE in SAS v 9.3 or higher.

Sensitivity analysis two: Tipping Point Analysis using PMM

The goal of the tipping point analysis is to determine how robust the results of the primary analysis are to varying its assumption that the change from baseline at Visit 7 AISRS total scores for subjects that discontinue early from the AR19 group is the same as the completers in the AR19 group. In particular, this analysis examines how altering this assumption to allow the discontinued subjects to have better and worse outcomes will impact the resulting estimates of the treatment effect. This will quantify the range of values which the assumptions can take on and still provide the same conclusions as the primary analysis, giving a very direct measure of the sensitivity of the primary analysis to deviations from the assumptions using an approach that has missing values for AR19 discontinuation subjects imputed. Missing AISRS total score data in the AR19 group will be imputed based on observed values in the AR19 group and likewise, missing AISRS total score values in the placebo group will be imputed based on observed values in the placebo group.

In this analysis, the estimate of the effect in the AR19 subjects may be viewed as a weighted average of the observed average for AR19 completers and the average MAR estimate for AR19 subjects. Shift values of .05 (treated subjects have 5% of the change from baseline AISRS total score as assumed in the primary methodology) through 1 (treated subjects have 100% of the change from baseline AISRS total score as assumed via the primary methodology) will be applied at increments of .05 and reported. The primary analysis will be rerun for all shift values and the resulting treatment difference, 97.5% CI and p-value for each shift value will be reported; the wider the range of values that result in no change in interpretation, the more robust the analysis results may be considered to be.

Subjects receiving placebo who discontinue prior to the end of the treatment period will have their change from baseline AISRS total score value imputed

based on the assumption that they respond to treatment in a similar manner to the placebo subjects who completed the study. For subjects receiving AR19 who discontinue prior to the end of the treatment period, the assumed response to treatment will be examined in increments from worst (subjects respond in a similar manner to the placebo subjects who completed the study) to best (subjects respond in a similar manner to the AR19 subjects who completed the study).

The steps to implement the tipping point analysis are as follows:

1) A mixed model repeated measures (MMRM) model will be run using all observed data and the LS mean in the AR19 group (20 and 40 mg/day separately) of change from baseline at Week 7 in AISRS total score will be calculated.

2) Missing data will be imputed based on the MAR assumption using multiple imputation procedure (PROC MI) to create 100 complete datasets with 20 burn-in iterations.

3) For subjects in the AR19 dose groups, the imputed values from Step 2 will be "penalized" by adding a percentage (i.e. 5%, 10%, 15%, 20%, etc. of the LS mean treatment difference) of the absolute value of the mean change calculated from Step 1; for the placebo group, no "penalty" will be taken for the imputed values.

4) Each newly generated complete dataset from Step 3 will be analyzed using the primary analysis MMRM model and results from all 100 datasets will be combined (PROC MIANALYZE) to generate inferences.

5) This analysis (Steps 3-4) will be repeated for a range of values (i.e. 5%, 10%, 15%, 20%, etc. of the treatment difference) until either the tipping point (where statistical significance of the treatment effect is lost) is identified or the 100% penalty is applied.

7.1.2 Assessment Time Windows

Data will be summarized based on the recorded visit; no visit windowing will be conducted. Visit 7 must be performed as scheduled based on the protocol, allowing for consistent and reliable efficacy measurements.

7.2 Efficacy Measurements

7.2.1 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. 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.

Each item is scored from a range of zero (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from zero to 54. Higher AISRS total scores signify greater severity of ADHD symptoms.

The following AISRS scores will be assessed:

- AISRS Hyperactivity/Impulsivity subscale score (sum of even numbered items 2 through 18)
- AISRS Inattentiveness subscale score (sum of odd numbered items 1 through 17)
- AISRS total score (sum of all items)

See Appendix 14.2 for more details on these items. Missing or invalid data for individual questions will be handled by rules described in Section 7.1.1.1.

7.2.2 Clinical Global Impression Scale (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. The severity of a subject's ADHD symptoms will be rated on a 7-point scale ranging from 1 (normal) to 7 (among the most extremely ill subjects).

The subject's current disease status will be classified as follows:

1 = Normal, not at all ill.

2 = Borderline ill.

3 = Mildly ill.

4 = Moderately ill.

5 = Markedly ill.

6 = Severely ill.

7 = Among the most extremely ill subjects.

The subject's disease improvement relative to Baseline (Visit 2) will be classified as follows:

1 = Very much improved.

2 = Much improved.

3 = Minimally improved.

4 = No change.

5 = Minimally worse.

6 = Much worse.

7 = Very much worse.

7.2.3 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. The MINI will be completed at Screening.

7.2.4 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. The CAADID will be completed at Screening.

7.2.5 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. 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 Index (BRI) and Metacognition (MI), and these indexes form the overall summary score, the Global Executive Composite (GEC). The BRIEF-A will be completed at Baseline (Visit 2) and Visit 7.

The BRIEF-A subscales, indices and overall summary score are scored as follows:

- BRIEF-A Inhibit subscale score (sum of items 5,16, 29, 36, 43, 55, 58, 73)
- BRIEF-A Self-Monitor subscale score (sum of items 13, 23, 37, 50, 64, 70)
- BRIEF-A Plan/Organize subscale score (sum of items 9, 15, 21, 34, 39, 47, 54, 63, 66, 71)
- BRIEF-A Shift subscale score (sum of items 8, 22, 32, 44, 61, 67)
- BRIEF-A Initiate subscale score (sum of items 6, 14, 20, 25, 45, 49, 53 62)
- BRIEF-A Task Monitor subscale score (sum of items 2, 18, 24, 41, 52, 75)
- BRIEF-A Emotional Control subscale score (sum of items 1, 12, 19, 28, 33, 42, 51, 57, 69, 72)
- BRIEF-A Working Memory subscale score (sum of items 4, 11, 17, 26, 35, 46, 56, 68)
- BRIEF-A Organization of Materials Subscale Score (sum of items 3, 7, 30, 31, 40, 60, 65, 74)
- BRIEF-A Behavioral Regulation Index (BRI) (sum of Inhibit, Shift, Emotional Control, Self-Monitor subscale scores)
- BRIEF-A Metacognition Index (MI) (sum of Initiate, Working Memory, Plan/Organize, Task Monitor, Organization of Materials subscale scores)
- BRIEF-A Global Executive Composite (GEC) Score (sum of BRI and MI scores)

7.2.6 Difficulties in Emotional Regulation Scale (DERS)

The DERS is a validated non-disease state scale consisting of 36 items scored on a range of 1 (almost never) to 5 (almost always). 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. The DERS will be completed at Baseline (Visit 2) and Visit 7.

The following DERS scores will be assessed:

- DERS Non-acceptance subscale score (sum of items 11, 12, 21, 23, 25, 29)
- DERS Goals subscale score (sum of items 13, 18, 20R, 26, 33)
- DERS Impulse subscale score (sum of items 3, 14, 19, 24R, 27, 32)
- DERS Awareness subscale score (sum of items 2R, 6R, 8R, 10R, 17R, 34R)
- DERS Strategies subscale score (sum of items 15, 16, 22R, 28, 30, 31, 35, 36)
- DERS Clarity subscale score (sum of items 1R, 4, 5, 7R, 9)
- DERS total score (sum of all subscale scores)

Note: “R” indicates a reverse-scored item which is calculated by subtracting the item score rather than adding.

7.2.7 Affective Style Questionnaire (ASQ)

The ASQ is a 20-item questionnaire used to measure individual styles in emotional regulation scored on a range of 1 (not true of me at all) to 5 (extremely true of me). 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. The ASQ will be completed at Baseline (Visit 2) and Visit 7.

The following ASQ scores will be assessed:

- ASQ Concealing subscale score (sum of items 1, 5, 9, 10, 13, 15, 18, 20)
- ASQ Adjusting subscale score (sum of items 2, 4, 7, 8, 12, 16, 19)

- ASQ Tolerating subscale score (sum of items 3, 6, 11, 14, 17)
- ASQ Total score (sum of all items)

7.3 Efficacy Outcomes

7.3.1 Primary Efficacy Outcome – AISRS total score

The primary efficacy analysis will be performed on the FAS population. The primary efficacy outcome is the change in AISRS total score from Visit 2 (Baseline) to Visit 7 (End of Study) in AR19 treated subjects compared to placebo.

7.3.2 Secondary Efficacy Outcomes

The primary analysis will be repeated on the PP population using the MMRM analysis described in Section 7.4.1.

The secondary efficacy outcomes include:

- 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

7.3.3 Additional Efficacy Outcomes

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.

7.4 Analysis Methods

7.4.1 Primary Efficacy Analyses – AISRS Total Scores

The primary efficacy analysis will be performed on the FAS population. The primary efficacy outcome is the change from baseline in AISRS total score at Visit 7 (Week 5) in AR19 (20 and 40 mg/day) versus 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.

The key elements of the primary efficacy analysis are as follows:

Data: AISRS total scores measured at Baseline through Visit 7. All available data will be used; there will be no imputation of missing data.

Model: Restricted maximum likelihood (REML)-based MMRM analysis

Fixed effects: The following fixed effects are planned:

- Treatment (class effect: AR19 20 mg/day, AR19 40 mg/day, placebo)
- Week (class effect: Weeks 1, 2, 3, 4, 5)
- Baseline AISRS total score
- Treatment-by-week interaction

Residual Variance-Covariance Matrix: An unstructured correlation matrix will be used to model the within-patient errors and restricted maximum likelihood estimation will be used. The Kenward-Roger method will be used for the denominator degrees of freedom. Should the model fail to converge with an unstructured covariance matrix, alternative covariance structures will be applied, in the following order, until the model converges: heterogeneous Toeplitz, heterogeneous compound symmetry, then heterogeneous autoregressive(1).

The null hypothesis:

H_0: Change from baseline AISRS total scores at Visit 7 are the same for AR19 and placebo

will be tested against the two-sided alternative hypothesis

H_1: Change from baseline AISRS totals scores at Visit 7 are not the same for AR19 and placebo.

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.

The estimand of this primary efficacy analysis is the mean treatment difference, AR19 (20 mg/day and 40 mg/day) vs. placebo, of change from baseline in AISRS total scores among all randomized subjects who remain in the study for the duration of the blind treatment period, regardless of treatment adherence.

7.4.2 Secondary Efficacy Analyses

The primary analysis will be repeated on the FAS population using the mixed model repeated measures analysis described in Section 7.4.1.

The secondary efficacy outcomes include:

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

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.

7.5 Other Efficacy Analyses

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.

7.6 Examination of Subgroups

The primary and secondary efficacy analyses (CGI and BRIEF-A composite scores only) will be repeated on the FAS population based on the following subgroups:

- Sex (Male, Female)
- Race (White, Black or African American, Other)
- ADHD type (Hyperactive-Impulsive, Inattentive, Combined)

8. SAFETY EVALUATION

All subjects who enter the study will be assessed for safety. Safety will be monitored by AEs assessed at each post-dose visit, physical examination, vital signs, electrocardiogram and clinical laboratory tests. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered at Screening, Baseline and all subsequent scheduled visits to assess emergent suicidal thoughts or behaviors.

8.1 Overview of Safety Analysis Issues

Missing end dates for AEs will not be imputed. If end date information is not available, it will be assumed that the finding or event is ongoing.

Missing AE start dates will be imputed based on the following rules:

- If only the year is known, the date will be set to 01 January of that year. If the year is the same as the year of the first dose of study medication, the date will be set to the date of the first dose of study medication.

- If the year and month are known the date will be set to first day of the month. If the year and month are the same as the year and month of the first dose of study medication, the date will be set to the date of the first dose of study medication.

- If the start date is completely missing it will be set to the date of the first dose of study medication.

8.2 Overview of Safety Analysis Methods

All safety data will be analyzed descriptively using the Safety population described in Section 4.1.1.

8.3 Extent of Exposure

The length of exposure (in days) of study medication will be calculated based on the dates of first and last dosing of study medication (last dosing date - first dosing date + 1), by treatment and overall. Length of exposure will be summarized by treatment group on the Safety population as continuous values and for the following categories (which correspond to scheduled study visit timing): 1-7 days, 8-14 days, 15-21 days, 22-28 days, and >=29 days.

8.4 Adverse Events

All AEs will be coded using MedDRA Version 21.0.

An AE is considered treatment-emergent, if it started on or after the first dose of study medication is administered. If a subject terminates early from the study and has an AE after his/her last dosing date, the AE will be deemed as treatment-emergent if it occurs ≤ 24 hours after the last dose and not as treatment-emergent if it occurs > 24 hours after the last dose of study medication. AEs with partial start dates will be imputed as outlined in Section 8.1.

Summary Tabulations

An overview of the frequency, i.e., the number and percentage of subjects with at least one of the following AEs will be presented by treatment group:

- Treatment-emergent adverse events (TEAEs).

- TEAEs related to study medication.
- Severe TEAEs.
- Serious treatment emergent AEs (SAEs).
- SAEs related to study medication.
- AEs leading to death.
- AEs leading to premature withdrawal of study medication.

System Organ Class/Preferred Term Tabulations

The frequency of subjects reporting TEAEs will be summarized within each system organ class (SOC), preferred term (PT), and treatment group. The SOC terms and PTs will be presented in decreasing order of the total number of subjects (frequency) who experienced each adverse event. System organ class terms and PTs with the same frequency will be presented alphabetically.

If a single subject experiences the same AE more than once, the subject will be counted once per SOC and PT for that AE, using the most severe intensity or highest relationship to study medication.

The frequency of subjects reporting the following TEAEs will be presented:

- All TEAEs.
- All TEAEs by intensity.
- All TEAEs by relationship to study drug.
- All treatment-emergent SAEs.
- All TEAEs leading to premature discontinuation from study.

By-Subject Listings

By-subject listings including relevant information (i.e. treatment, age, sex, race, duration of AE, severity, relationship, outcome, action taken, etc.) will be presented for:

- All AEs.

- SAEs.
- AEs leading to death.
- AEs leading to premature discontinuation of study medication.

The onset of AEs will be calculated relative to the first dose of study medication. The duration of AEs in days will be calculated as the difference between the onset and resolution dates of the AE. If the AE is ongoing at the end of the study, or the resolution date is unknown, the duration will be presented as 'Unknown'.

8.5 Clinical Laboratory Evaluations

The following laboratory tests will be performed:

- 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.
- 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.
- 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.
- 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, tetrahydrocannabinol (THC)/cannabis, and phencyclidine (PCP).

All laboratory values will be presented in data listings indicating abnormal values for non-fasting serum chemistry, CBC, genetic testing, and tests for drugs of abuse; and positive values for pregnancy tests.

8.6 Physical Examinations

A full physical examination will be performed at Visits 1 (Screening), 7 (End of Study), and at an Early Termination Visit, if necessary. Although not scheduled, a full physical examination may be performed at any time (post-screening) for safety reasons. The following body areas and systems will be examined: head and neck, abdominal, chest, cardiovascular, heart, respiratory, musculoskeletal, skin, neurological and endocrine. Body weight will 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.

Abnormal physical examination results performed prior to first dose of study drug will be summarized descriptively in the medical history table by treatment group. Abnormal results obtained on or after the first dose of study drug will be presented in the applicable adverse event table(s).

8.7 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). Respiratory rate, height for BMI, and temperature will be measured at Screening (Visit 1) only.

Systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and temperature will be summarized descriptively for each visit, including change from Baseline (where applicable).

In addition, the incidence of sponsor defined potentially clinically significant (PCS) post-treatment vital sign values will be presented by treatment group and visit to examine the frequency and percentage of subjects that meet the PCS criteria outlined below:

- Heart Rate
    - ≥20 bpm increase
    - ≥20 bpm decrease
- Systolic Blood Pressure
    - ≥20 mmHg increase
    - ≥20 mmHg decrease
- Diastolic Blood Pressure

- ≥15 mmHg increase
- ≥15 mmHg decrease

- Weight
  - ≥5% increase
  - ≥5% decrease

8.8 Electrocardiogram

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 read by a central reader(s). Although not scheduled, an ECG assessment may be performed at any time (post-screening) for safety reasons. Final assessment of normal, abnormal results and clinical significance of the ECG, including the central reader's report, will be made by the investigator.

Screening ECG measurements, overall interpretation, and individual diagnoses will be summarized descriptively on the Safety population. All ECG measurements (including safety-related post-screening values) will be presented in data listings.

8.9 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (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.

The "Baseline/Screening" 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).

The frequency of suicidality using the C-SSRS will be summarized for each visit for each of the following outcomes:

- Number of subjects reporting at least one occurrence of suicidal ideation or behavior.
- Number of subjects reporting any type of suicidal behavior.

- Number of subjects reporting any type of suicidal ideation.

9. PHARMACOKINETIC EVALUATION

Exposure-response relationships using population pharmacokinetics will be explored. To aid the population pharmacokinetic analysis, two blood plasma samples will be collected from all subjects. 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). 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 pharmacokinetic analysis and reporting will be covered in a separate SAP and report.

10. OTHER ANALYSES

No other analyses are planned for this study. However, any additional analyses performed after finalization of the SAP will be considered exploratory and will be identified as such in the clinical study report (CSR).

11. INTERIM ANALYSES AND DATA MONITORING

No interim analyses or official data monitoring are planned for this study.

12. CHANGES TO STUDY CONDUCT OR ANALYSES PLANNED IN THE PROTOCOL

12.1 Changes in the Conduct of the Study

This SAP is based on Version 3.0 of the AR19.004 clinical study protocol dated August 20, 2018. No changes in the conduct of the study are planned from this version of the protocol.

12.2 Changes in the Analysis Planned in the Protocol

This SAP is based on Version 3.0 of the AR19.004 clinical study protocol dated August 20, 2018. No changes in the analyses of the study are planned from this version of the protocol.

13. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.
2. US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

3. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.

14. APPENDICES

14.1 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
Blood alcohol	X								
HbA1c	X								
HCV RNA[c]	X								
Pregnancy[d]	X	X		X		X	X		X
Urinalysis[e]	X						X		X
CYP 2D6 testing[d]		X							
Drugs of abuse test	X	X							
C-SSRS (BL/Screen)	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

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	
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.

[e] Hepatitis C virus RNA for subjects who report a positive history of hepatitis C that is now completely treated.

[f] Specific gravity, pH, urobilinogen, leucocyte esterase, nitrite, bilirubin, ketones, hemoglobin, glucose, and total protein; if the dipstick is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis including: WBC, RBC, epithelial cells, bacteria, yeast, crystals, hyaline casts, granular casts, mucous threads, and waxy casts.

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

14.2 Adult ADHD Investigator Symptom Rating Scale (AISRS) and Subscales

Subscale	Item
Hyperactivity/ Impulsivity	2. Fidget or squirm with hands or feet
	4. Leave seat in meetings or other
	6. Feel restless or fidgety
	8. Difficulty relaxing/unwinding
	10. Feel overly active compelled to do things
	12. Find yourself talking too much
	14. In conversation finish other's sentences
	16. Difficulty waiting your turn
	18. Interrupt others when they are busy
Inattentiveness	1. Careless mistakes working on boring projects
	3. Difficulty keeping attention
	5. Difficulty concentrating when spoken to
	7. Trouble wrapping up final details of project
	9. Difficulty getting things in order
	11. Avoid task that requires lots of thought
	13. Misplace or have difficulty finding things

	15. Find yourself being distracted by activity
	17. Problems remembering appointments