CLINICAL STUDY PROTOCOL

Title: Amphetamine Extended-Release Tablets in the Treatment of Adults with ADHD.

Protocol Number:	TRI108-ADD-400
Investigational Drug:	Amphetamine ER Tablets, 5, 10, 15, and 20 mg (Manufactured by Tris Pharma, Inc., U.S.A)
Version:	v. 3.1 (March 2019)
IND Applicant/Sponsor:	Tris Pharma, Inc. 2033 US 130 Monmouth Junction, NJ 08852
Authorized Signatory:	Barry K. Herman, MD, MMM Chief Medical Officer Tris Pharma, Inc.
Primary Study Contact:	Antonio Pardo, MD Associate Director, Clinical Affairs and Pharmacovigilance Tris Pharma, Inc.
Protocol Amendments:	N/A

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

INVESTIGATOR'S SIGNATURE

I have read this protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name

_____

Title

_____

Signature

_____

Date (mm/dd/yyyy)

SPONSOR'S SIGNATURE

Approved by:

Barry K. Herman MD, MMM Chief Medical Officer Tris Pharma, Inc.	Date (mm/dd/yyyy)

PROCEDURES IN CASE OF EMERGENCY

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SYNOPSIS

Title of Study	**Amphetamine Extended-Release Tablets in the Treatment of Adults with ADHD**
Study Number	**TRI108-ADD-400**
Study Center(s)	Multicenter (up to 3 sites)
Clinical Phase	Phase 3
Indication	ADHD (Attention-deficit/hyperactivity disorder)
Sample Size	Approximately 108 subjects – Maximum allowable cohort size of 18 subjects at up to 3 sites
Treatment Duration	~11 weeks
Main Entry Criteria	Adult male and female subjects aged 18 to 60 years who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD, otherwise healthy.
Test Product	Amphetamine Extended-Release Tablets (AMPH ER TAB), 5, 10, 15 or 20 mg (manufactured by Tris Pharma, Inc., USA)
Reference	Matching placebo including flavor, 5, 10, 15 or 20 mg (manufactured by Tris Pharma, Inc., USA)
Objectives	**Efficacy Objective:** To evaluate the efficacy of AMPH ER TAB compared to placebo in adult patients with ADHD aged 18–60 years. **Safety Objective:** To assess the safety and tolerability of AMPH ER TAB in adult patients with ADHD aged 18–60 years.
Methodology	This is a randomized, double-blind (DB), placebo-controlled, parallel, study to assess the efficacy and safety of AMPH ER TAB compared to placebo for the treatment of ADHD in adults aged 18 to 60 years. After Screening and Baseline evaluations are complete, eligible subjects will be randomized in the study to take DB AMPH ER TAB or matching placebo orally once daily in the morning beginning the day after the Baseline visit. There will be a 5-week DB dose titration phase. The starting dose of AMPH ER TAB or matching placebo will be 5 mg in the morning before 10 am, with or without food, swallowed whole or chewed. Subjects will then be titrated up by 5 mg increments each week. After Visit 3 subjects will receive a final dose of 20 mg for 14 (± 3) days prior to Visit 5. Subjects who cannot tolerate the study drug will be discontinued from the study. A Permanent Product Measure of Performance (PERMP) placement test will be done at Screening or at Baseline. PERMP practice sessions will be done before and after efficacy and safety assessments during Baseline and Visits 1 to 3. An abbreviated administration of serial PERMPs will take place at Visit 4 where PERMP will be administered at pre-dose, 0.5, 1, 2 and 4 hours post-dose. At Visit 5, efficacy assessments will include the administration of serial PERMPs at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose. Adult Investigator Symptom Rating Scale (AISRS) and Clinical Global Impression Scale-Severity (CGI-S) will be conducted at Baseline and Visits 1 to 5. Digit Symbol Substitution Test (DSST) will be administered at Baseline and Visit 5.

	Safety assessments will include treatment-emergent adverse events, physical examination, vital signs, body weight, Columbia Suicide Severity Rating Scale (C-SSRS), and direct questioning to assess for sleep, appetite, mood and psychotic events.
Inclusion/ Exclusion Criteria	Inclusion Criteria Subjects must meet all of the following criteria to be considered eligible to participate in the study: 1. Male or female aged 18 to 60 years, inclusive at the time of Screening. 2. Diagnosed with ADHD using the DSM-5 criteria based on the Adults ADHD Clinical Diagnostic Scale (ACDS). 3. IQ within normal range based upon clinical opinion of the Investigator. 4. Baseline AISRS total score greater than or equal to 26. 5. Baseline score of 4 or higher in CGI-S. 6. Females who participate in this study will be of childbearing or non-childbearing potential: • Childbearing potential: Physically capable of becoming pregnant • Non-childbearing potential: o Permanently sterile (i.e., both ovaries removed, uterus removed, or bilateral tubal ligation for at least 6 weeks or documented successful hysteroscopic sterilization); and/or o Post-menopausal (no menstrual period for at least 12 consecutive months without any other medical cause). 7. Females of childbearing potential must be non-lactating and must have a negative serum pregnancy test at Screening. 8. Willing to use acceptable, effective methods of contraception. 9. Be able to attend the clinic regularly and reliably. 10. Be able to understand, read, write, and speak English fluently to complete the study-related materials. 11. Be informed of the nature of the study and give written consent prior to any study procedure.
	Exclusion Criteria 1. Current or lifetime history of bipolar disorder or any psychotic disorder as established by Mini International Neuropsychiatric Interview (M.I.N.I.) 7.0.2. 2. Current history of major depression generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, or post-traumatic stress disorder as established by the M.I.N.I. 7.0.2. 3. Known history of chronic medical illnesses including untreated thyroid disease, peripheral vasculopathy, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy, and known family history of sudden death. 4. History of uncontrolled hypertension or a resting systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. Subjects with well-controlled hypertension on a stable dose for at least 3 months of anti-hypertensives will be allowed to participate.

	5. Have clinically significant findings in vital signs measurements at Screening including: • Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg • Heart rate >100 bpm 6. Known history or presence of significant renal or hepatic disease, as indicated by clinical laboratory assessment (clinically significant liver function tests, blood urea nitrogen, or creatinine levels) 7. Clinically significant abnormal electrocardiogram or cardiac findings on physical examination (including the presence of a pathologic murmur). 8. Use of the following medications within 14 days of Baseline Visit: • Atomoxetine • Monoamine oxidase inhibitors (e.g., selegiline, isocarboxazid, phenelzine, tranylcypromine) • Tricyclic antidepressants (e.g., desipramine, protriptyline). 9. Use of the following medications within 3 days of Baseline Visit: • Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid hydrochloride [HCl], ascorbic acid) • Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts). 10. Use of fluoxetine within 30 days of Baseline Visit. 11. Use of stimulant medications within 1 week of Baseline Visit. 12. Planned use of prohibited drugs or agents from the Screening visit through the end of the study. 13. Participation in a clinical study in which an investigational drug was administered within 30 days prior to Screening. 14. Abnormal clinically significant laboratory test values at Screening that, in the opinion of the Medical Monitor or Sponsor, would preclude study participation. 15. Known history of allergy/hypersensitivity to amphetamine or any of the components of AMPH ER TAB. 16. Known history of lack of clinical response to amphetamine based upon Investigator judgment. 17. Positive test result for HIV, Hepatitis B surface antigen, or Hepatitis C antibody. 18. Any uncontrolled medical condition that, in the opinion of Medical Monitor or Sponsor, would preclude study participation. 19. History or presence of alcohol dependence or substance abuse disorder according to DSM-5 or within the last 12 months. 20. Subject's inability or unwillingness to follow directions from the study research staff. 21. Answer of "yes" to questions 4 or 5 of the C-SSRS within the last 2 years.

Assessments	• CGI-S • AISRS DSM-V Update • DSST • ACDS DSM-V Update • M.I.N.I. 7.0.2 • PERMP • C-SSRS • Questionnaire for Sleep, Appetite, Mood and Psychotic Adverse Events • Adverse Events • Electrocardiogram • Safety Labs • Physical Exam • Vital Signs • Body weight • Medical History • Concomitant Medications
Statistical Analysis	Efficacy: The primary efficacy estimand is defined by the following 3 components: a. Target population: adult patients with ADHD aged 18 to 60 years who can tolerate AMPH ER TAB at 20 mg once daily. b. Primary efficacy endpoint: PERMP-T score over all post-dose time points assessed during the administration of serial PERMPs at Visit 5 c. Measure of intervention effect: treatment difference in means averaged over all post-dose time points for endpoint described above between AMPH ER TAB and placebo in target population regardless of use of any concomitant medications. The primary efficacy endpoint will be assessed using a linear Mixed Model Repeated Measures (MMRM) analysis. This is a restricted maximum likelihood (REML)-based analysis implemented using SAS® PROC MIXED. The model will include treatment, time and treatment by time as fixed effects and subject as a random effect. Pre-dose PERMP-T score will be included as a covariate. The difference between AMPH ER TAB and placebo will be assessed at the alpha = 0.05 level of significance. The covariance structure used in the final MMRM model will be the one that has the lowest Akaike Information Criterion (AIC) among the following selections: SP(POW), unstructured, compound symmetry (CS), heterogeneous CS or heterogeneous Toeplitz. Kenwood-Roger correction will be used to estimate denominator degrees of freedom. The treatment effect is estimated by the overall adjusted least square mean difference between two treatment groups. 95% CI for the adjusted

	least square mean will be constructed and p-value for the treatment comparison will also be provided. Key secondary efficacy outcomes as determined by the comparison of each PERMP-T score at each time point (0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose) with pre-dose PERMP-T scores at Visit 5 are: • Onset of clinical effect • Duration of clinical effect The key secondary outcomes of onset and duration of efficacy (clinical effect) of AMPH ER Tab vs. placebo will be tested using the same MMRM analysis as performed on the primary efficacy variable. Additional secondary efficacy outcomes will be: • Change from Baseline in AISRS scores at each post-baseline visit • Change from Baseline in CGI-S at each post-baseline visit • Change from Baseline in DSST at Visit 5 A detailed statistical analysis plan will be written and finalized prior to unblinding of the data.
	<u>Safety:</u> The Safety Population will include all subjects who receive ≥1 dose of AMPH ER TAB or matching placebo and had at least one assessment after dosing. Safety assessments will include treatment-emergent adverse events, physical examination, vital signs, body weight, Columbia Suicide Severity Rating Scale (C-SSRS), and direct questioning to assess for sleep, appetite, mood and psychotic adverse events. Statistical analysis of safety: Safety parameters will be reported using descriptive statistics.

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LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
ACDS	Adults ADHD Clinical Diagnostic Scale
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AISRS	Adult Investigator Symptom Rating Scale
AR	Adverse reaction
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression Scale–Severity
cGMP	Current Good Manufacturing Practice
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double-blind
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram/electrocardiography
EDC	Electronic Data Capture
ER	Extended Release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
ICH	International Conference for Harmonisation
ID	Identification
IND	Investigational New Drug
IR	Immediate release
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System

Abbreviation or specialist term	Explanation
MAOI	Monoamine oxidase inhibitors
M.I.N.I. 7.0.2	Mini International Neuropsychiatric Interview 7.0.2
MMRM	Mixed Effect Model Repeat Measurement
MedDRA	Medical Dictionary for Regulatory Activities
PERMP	Permanent Product Measure of Performance
PP	Per-Protocol Population
RAND	Randomized Population
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Background

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by pervasive impairment in symptoms of inattention, hyperactivity, and impulsivity[1]. Symptoms of ADHD typically manifest in early childhood, often leading to diagnosis and treatment. Recent prevalence data indicate approximately 9.4% of children 2 to 17 years of age are diagnosed with ADHD[2]. Even with current psychopharmacologic treatment, ADHD can persist into adulthood, with a reported 40 to 66% of individuals diagnosed with ADHD as a child continuing to show symptoms of ADHD as an adult[3,4]. The prevalence of adult ADHD in the United States in 2006 was 4.4%[5]. Adult ADHD is associated with impairments in activities of daily living, including educational attainment, social interacting, and disrupted or poor work performance[6-9]. Difficulties adhering to medication regimens have been noted in patients with ADHD[10]. ADHD poses safety risks with higher rates of accidents associated with driving and operating heavy machinery[8,9,11,12]. Diagnosis of ADHD is based on a complete evaluation of the patient, and assessments based on criteria published in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1].

1.2 Pharmacotherapy

Clinical practice guidelines recommend a combination of behavior therapy and psychostimulant medication for treatment of ADHD in children, adolescents, and adults[13,14]. Psychostimulants are commonly prescribed for ADHD in adults[15], and amphetamine is considered to be a first-line treatment for this population[15]. As adult patients seek symptomatic improvement during the work day and into the early evening hours, with fewer required doses, ER formulations are often considered as a first-line treatment option. Patients with ADHD may frequently require supplemental (immediate-release [IR]) stimulant medication for maximum treatment efficacy, resulting in lowered compliance (due to the need for frequent administration of multiple medications at varying dosages). Patients taking multiple doses of varying psychostimulant medications also may face social stigmas associated with frequent medication use[16]. The demands of work environment and personal and family life, coupled with the need for a simple medication strategy, suggest that adults with ADHD will benefit from a once-daily psychostimulant medication with an extended duration of effect.

1.3 Amphetamine Extended-Release Tablets

Amphetamine is a well-established therapeutic agent for the treatment of ADHD. Since the original Food and Drug Administration (FDA) approval of amphetamine for ADHD, various forms have been approved for use (both IR dosage forms, oral solution, and tablets, and ER dosage forms, capsules, and tablets with various release technologies).

Amphetamine Extended-Release Tablets (AMPH ER TAB) is an ER tablet formulation of a combination of 3 well-established and well-characterized racemic mixtures of *d*, *l* amphetamine sulfate, *d*, *l*-amphetamine aspartate monohydrate, and dextroamphetamine sulfate. The *d*, *l* amphetamine sulfate and the dextroamphetamine sulfate are bound to polistirex, a sodium polystyrene sulfonate. This amphetamine polymer complex is further coated with a flexible, semi-permeable coating material that provides for the gradual release of amphetamine. The final drug product is prepared by adding a specific ratio of coated

amphetamine-ion exchange polymer complex, uncoated amphetamine-ion exchange polymer complex, and unbound amphetamine salts (amphetamine aspartate monohydrate and dextroamphetamine sulfate)[17].

No product-specific non-clinical pharmacology or toxicology studies have been conducted for AMPH ER TAB.

AMPH ER TAB formulation will be available in 4 strengths: 5, 10, 15, and 20 mg. AMPH ER TAB (20 mg) showed comparable bioavailability in 29 healthy adults with respect to both *d*- and *l*-amphetamine, when administered as a chewable tablet or swallowed whole, compared to an equivalent 20 mg dose of the reference product, DYANAVEL® XR (amphetamine) ER Oral Suspension, 2.5 mg/mL, (Tris Pharma, Inc., USA), under fasted conditions[17]. The results also supported the absence of food effect on AMPH ER TAB when administered as a chewable tablet. The bioavailability of *d*- and *l*-amphetamine was comparable after administration of AMPH ER TAB when administered as a chewable tablet compared to being swallowed whole under fasted conditions[17].

Lastly, the concentration versus time profiles following single-dose administration of AMPH ER TAB suggests that the test product meets the goals of once-daily dosing, without any indicative potential of dose dumping upon repeated administration[17].

Safety findings in the study were consistent with that reported previously for other amphetamine products[17].

The purpose of this study is to evaluate the efficacy, safety, and tolerability of AMPH ER TAB compared to placebo in adults with ADHD aged 18 to 60 years.

2 OBJECTIVES

2.1 Efficacy Objective

To evaluate the efficacy of AMPH ER TAB compared to placebo in adult patients with ADHD aged 18 to 60 years.

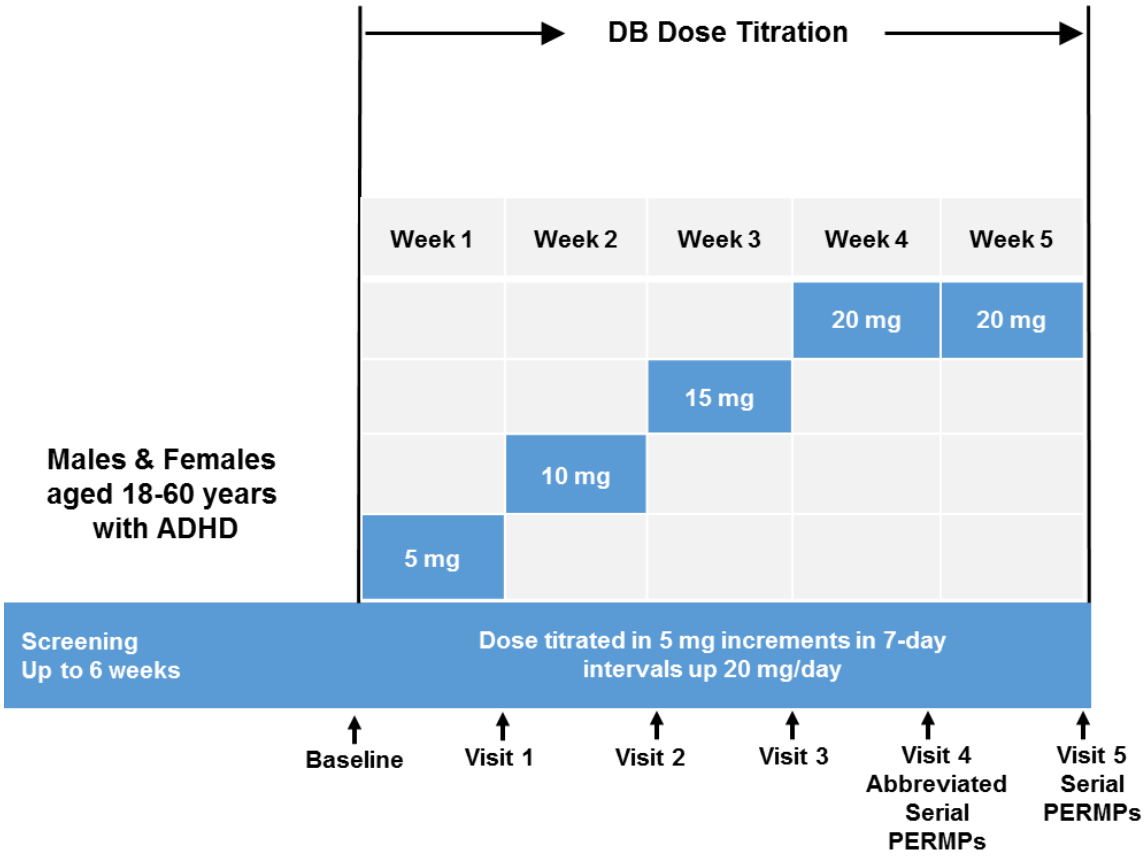
2.2 Safety Objective

To assess the safety and tolerability of AMPH ER TAB in adult patients with ADHD aged 18 to 60 years.

3 STUDY DESIGN

3.1 Design

Figure 1: Study Design



This is a randomized, double-blind (DB), placebo-controlled, parallel, study to assess the efficacy and safety of AMPH ER TAB compared to placebo for the treatment of ADHD in adults aged 18 to 60 years.

After Screening and Baseline evaluations are complete, eligible subjects will be randomized to take double-blinded (DB) AMPH ER TAB or matching placebo orally once daily in the morning beginning the day after the Baseline visit.

There will be a 5-week DB dose titration phase. The starting dose of AMPH ER TAB or matching placebo will be 5 mg in the morning before 10 am, with or without food, swallowed whole or chewed. Subjects will then be titrated up by 5 mg increments each week. After Visit 3 subjects will receive a final dose of 20 mg for 14 (± 3) days prior to Visit 5. Subjects who cannot tolerate the study drug will be discontinued from the study.

A Permanent Product Measure of Performance (PERMP) placement test will be done at Screening or Baseline. PERMP practice sessions will be done before and after efficacy and safety assessments during

Baseline and Visits 1 to 3. An abbreviated administration of serial PERMPs will take place at Visit 4 where PERMP will be administered at pre-dose, 0.5, 1, 2 and 4 hours post-dose.

At Visit 5, efficacy assessments will include the administration of serial PERMPs at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose.

AISRS and CGI-S will be conducted at Baseline and Visits 1 to 5. DSST will be administered at Baseline and Visit 5.

Safety assessments will include treatment-emergent adverse events, physical examination, vital signs, body weight, Columbia Suicide Severity Rating Scale (C-SSRS), and direct questioning to assess for sleep, appetite, mood and psychotic adverse events.

A schematic of the overall study design is presented in Figure 1.

The full schedule of events is found in Appendix A.

This study will be conducted in the United States.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

The PERMP is a validated, time-sensitive, skill-adjusted test consisting of simple math problems to be completed at multiple time points (administration of serial PERMPs). The PERMP Total or PERMP-T score is the sum of the number of math problems attempted plus the number of math problems answered correctly and it provides an objective measure of performance that is time-sensitive, ADHD medication-sensitive, and well documented as a measure to evaluate ADHD medication effectiveness throughout the day. The PERMP score range from 0-800 with higher scores indicating better performance.

The primary efficacy estimand is defined by the following 3 components:

a. Target population: adult patients with ADHD aged 18 to 60 years who can tolerate AMPH ER TAB at 20 mg once daily.

b. Primary efficacy endpoint: PERMP-T score over all post-dose time points assessed during the administration of serial PERMPs at Visit 5

c. Measure of intervention effect: treatment difference in means averaged over all post-dose time points for endpoint described above between AMPH ER TAB and placebo in target population regardless of use of any concomitant medications.

The primary efficacy endpoint will be assessed using a linear MMRM model using SAS® PROC MIXED. The model will include treatment, time and treatment by time as fixed effects and subject as a random effect. Pre-dose PERMP-T score will be included as a covariate. The difference between AMPH ER TAB and placebo will be assessed at the alpha = 0.05 level of significance.

3.2.2 Secondary Endpoints

Key secondary efficacy outcomes as determined by the comparison of each PERMP-T score at each time point (0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose) with pre-dose PERMP-T scores at Visit 5 are:

- Onset of clinical effect
- Duration of clinical effect

The key secondary outcomes of onset and duration of efficacy (clinical effect) of AMPH ER Tab vs. placebo will be tested using the same MMRM analysis as performed on the primary efficacy variable.

Additional secondary efficacy outcomes will include:

- Change from Baseline in CGI-S at each post-baseline visit
- Change from Baseline in AISRS scores at each post-baseline visit
- Change from Baseline in DSST at Visit 5

3.2.3 Safety Endpoint

Safety will be monitored by adverse events (AEs) assessed at each visit.

Medical history will capture all medical conditions at the Screening visit. Physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests will be conducted as described on Appendix A, or at the discretion of the Principal Investigator.

In addition, the following assessments will be conducted at Baseline and all subsequent scheduled visits: C-SSRS, vital signs (BP and HR), body weight and direct questioning to assess for sleep, appetite, mood and psychotic adverse events.

3.3 Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Male or female aged 18 to 60 years, inclusive at the time of Screening.
2. Diagnosed with ADHD using the DSM-5 criteria based on the Adults ADHD Clinical Diagnostic Scale (ACDS).
3. IQ within normal range based upon clinical opinion of the Investigator.
4. Baseline AISRS total score greater than or equal to 26.
5. Baseline score of 4 or higher in CGI-S.
6. Females who participate in this study will be of childbearing or non-childbearing potential:
    - Childbearing potential: Physically capable of becoming pregnant
    - Non-childbearing potential:
        - Permanently sterile (i.e., both ovaries removed, uterus removed, or bilateral tubal ligation for at least 6 weeks or documented successful hysteroscopic sterilization); and/or

- Post-menopausal (no menstrual period for at least 12 consecutive months without any other medical cause).

7. Females of childbearing potential must be non-lactating and must have a negative serum pregnancy test at Screening.
8. Willing to use acceptable, effective methods of contraception.
9. Be able to attend the clinic regularly and reliably.
10. Be able to understand, read, write, and speak English fluently to complete the study-related materials.
11. Be informed of the nature of the study and give written consent prior to any study procedure.

3.4 Exclusion Criteria

The presence of any of the following exclusion criteria precludes a subject from study enrollment:

1. Current or lifetime history of bipolar disorder or any psychotic disorder as established by Mini International Neuropsychiatric Interview (M.I.N.I.) 7.0.2.
2. Current history of major depression generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, or post-traumatic stress disorder as established by the M.I.N.I. 7.0.2.
3. Known history of chronic medical illnesses including untreated thyroid disease, peripheral vasculopathy, known structural cardiac disorders, serious cardiac conditions, serious arrhythmias, cardiomyopathy, and known family history of sudden death.
4. History of uncontrolled hypertension or a resting systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. Subjects with well-controlled hypertension on a stable dose for at least 3 months of anti-hypertensives will be allowed to participate.
5. Have clinically significant findings in vital signs measurements at Screening including:
    - Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg
    - Heart rate >100 bpm
6. Known history or presence of significant renal or hepatic disease, as indicated by clinical laboratory assessment (clinically significant liver function tests, blood urea nitrogen, or creatinine levels)
7. Clinically significant abnormal electrocardiogram or cardiac findings on physical examination (including the presence of a pathologic murmur).
8. Use of the following medications within 14 days of Baseline Visit:
    - Atomoxetine
    - Monoamine oxidase inhibitors (e.g., selegiline, isocarboxazid, phenelzine, tranylcypromine)
    - Tricyclic antidepressants (e.g., desipramine, protriptyline).
9. Use of the following medications within 3 days of Baseline Visit:

- Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid hydrochloride [HCl], ascorbic acid)
- Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts).

10. Use of fluoxetine within 30 days of Baseline Visit.
11. Use of stimulant medications within 1 week of Baseline Visit.
12. Planned use of prohibited drugs or agents from the Screening visit through the end of the study.
13. Participation in a clinical study in which an investigational drug was administered within 30 days prior to Screening.
14. Abnormal clinically significant laboratory test values at Screening that, in the opinion of the Medical Monitor or Sponsor, would preclude study participation.
15. Known history of allergy/hypersensitivity to amphetamine or any of the components of AMPH ER TAB.
16. Known history of lack of clinical response to amphetamine based upon Investigator judgment.
17. Positive test result for HIV, Hepatitis B surface antigen, or Hepatitis C antibody.
18. Any uncontrolled medical condition that, in the opinion of Medical Monitor or Sponsor, would preclude study participation.
19. History or presence of alcohol dependence or substance abuse disorder according to DSM-5 or within the last 12 months.
20. Subject's inability or unwillingness to follow directions from the study research staff.
21. Answer of "yes" to questions 4 or 5 of the C-SSRS within the last 2 years.

3.5 Effective Methods of Contraception

Subjects participating in this study must use an acceptable single- or double-method of contraception as defined below:

- Females: from 21 days prior to Baseline until 28 days after Visit 5
- Males: from Baseline until 28 days after Visit 5

Table 1: Acceptable Effective Methods of Contraception

Single-Method	Double-Method (must use at least two)	
Surgically sterile	Diaphragm	Condom
Post-menopausal	Cervical cap	Spermicide
Remain abstinent	Vaginal sponge	Vasectomy
	Non-hormonal IUD	Hormonal contraception
Hormonal contraception includes: Oral contraceptives, intravaginal devices, hormonal IUD, injections, transdermals, and implants		

3.6 Subject Withdrawal Criteria

Within the provisions of informed consent and good clinical judgment with respect to the subject's safety, every attempt should be made to have subjects complete the study. The following are possible reasons to terminate the participation of any subject from the study:

- Signs and symptoms of intolerance to the study medication.
- A treatment-related, serious adverse event (SAE) is observed.
- The subject is grossly non-compliant, as determined by the Investigator.
- Continued participation, in the opinion of the Investigator, is no longer in the best interest of the subject.
- The subject wishes to withdraw for any reason.
- Unblinding of the Investigator, site personnel performing assessments, or subject to a subject's treatment assignment.

Subjects will be encouraged to adhere to the protocol and complete all required assessments for the study. A subject may also be discontinued from the study for any of the following medical and/or administrative reasons:

- Pregnancy
- At the discretion of the Investigator at any time
- At the subject's request
- Occurrence of a Treatment Emergent Adverse Event (TEAE) or considerable worsening of an AE that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the Investigator or the Sponsor. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.

Any enrolled subjects desiring to discontinue prior to study completion should be encouraged to continue in the study and adhere to the protocol and subsequent regularly scheduled safety and effectiveness evaluations. Subjects who are discontinued outside of any scheduled visit will be encouraged to complete the final study visit at the time of withdrawal. Subjects who are discontinued during a scheduled visit will be encouraged to complete all assessments for both that study visit and the final study visit at the time of withdrawal. A subject who withdraws following study drug administration will not be replaced in their cohort.

3.7 Study Stopping Rules

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.

4 STUDY SCHEDULE AND PROCEDURES

4.1 Study Schedule

The study schedule table can be found in Appendix A.

4.2 Efficacy and Safety Assessments

4.2.1 Permanent Product Measurement of Performance (PERMP)

The PERMP is a validated, time-sensitive, skill-adjusted test consisting of simple math problems to be completed at multiple time points (administration of serial PERMPs) and is a robust, objective measure of the ability to initiate a task, self-monitor/stay on task, and complete written seatwork[18]. The PERMP does not test for mathematical ability or the ability to learn math because the difficulty of problems is adjusted to the existing math skill level of each participant to ensure that each individual achieves high accuracy rates.

A PERMP placement test will be done at Screening or at Baseline to determine the appropriate level of math test difficulty. PERMP practice sessions will be done before and after efficacy and safety assessments during Baseline and Visits 1 to 3. An abbreviated administration of serial PERMPs will take place at Visit 4 where PERMP will be administered at pre-dose, 0.5, 1, 2 and 4 hours post-dose.

At Visit 5 administration of serial PERMPs will be done at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose.

Training on the PERMP will be required to all personnel assigned to perform this study assessment. A designated, qualified individual from the study research team will perform the assessment.

4.2.2 Adults ADHD Clinical Diagnostic Scale (ACDS) DSM-V Update

The ACDS will be used to determine study eligibility. An ACDS assessment will be done at Screening and/or Baseline. The Investigator or other designated, qualified individual from the study research team will perform the assessment.

4.2.3 Mini International Neuropsychiatric Interview (M.I.N.I.) 7.0.2

The M.I.N.I. 7.0.2, a validated, structured diagnostic interview, will be administered at Baseline or Screening to confirm exclusions 1 and 2. The M.I.N.I. 7.0.2 may be administered by a psychiatrist or PhD-level psychologist. Other staff must be approved by Sponsor to administer the M.I.N.I. 7.0.2.

4.2.4 Adult Investigator Symptom Rating Scale (AISRS) DSM V Update

The AISRS will be used to determine study eligibility and as additional efficacy scale during Visits 1 to 5[19].

4.2.5 Clinical Global Impression Scales

The Clinical Global Impression Scales are used to measure features associated with ADHD. A global assessment of disease severity (CGI-S) will be done at the Screening, Baseline, and at Visits 1 to 5. The Investigator or other designated, qualified individual from the study research team will perform the assessment.

4.2.6 Digit Symbol Substitution Test (DSST)

The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key located on the top of the page. The DSST is sensitive to the presence of cognitive dysfunction as well as to change in cognitive function[20]. This assessment will be done at Baseline, and at Visit 5.

4.2.7 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[21].

The baseline version of the C-SSRS will be administered to all subjects at Screening. The "Since Last Visit" version will be used at all subsequent study visits (and Early Termination, if applicable). The Investigator or other designated, qualified individual from the study research team will perform the assessment.

4.2.8 Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events

Refer to Appendix B *Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events*. This assessment will be administered at Baseline and Visits 1 to 5.

4.2.9 Study Visits and Procedures

All study visit assessments will be collected on electronic case report forms (eCRF).

Safety will be monitored by observation of and direct inquiry regarding AEs at Screening, Baseline, and each post-dose visit. Subjects may experience AEs that necessitate an unscheduled visit. Situations may also arise wherein the Investigator asks a subject to report for an unscheduled visit (UNS) following the report of an AE or SAE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of subjects during the study. All eCRFs should be completed for each unscheduled visit. Refer to Section 8.3 for information on AE collection, recording, and reporting.

Medical history will capture all medical conditions at the Screening visit. Physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests will be conducted as described on Appendix A, or at the discretion of the Principal Investigator.

In addition, the C-SSRS will be administered at Screening, Baseline, and all subsequent scheduled visits to assess emergent suicidal thoughts or behaviors. Vital signs (BP and HR), body weight and direct questioning to assess for sleep, appetite, mood and psychotic events will be conducted at Baseline and Visits 1 to 5. The Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events will be administered at Baseline and all subsequent scheduled visits.

During Visit 5, subjects who are smokers will be allowed to have up to 3 cigarette breaks.

4.2.10 Study Periods

Study duration is up to 11 weeks consisting of the following:

- Screening (up to 6 weeks prior to Baseline)
- Baseline

- Visits 1 to 3 (DB Titration)
- Visit 4 (Abbreviated administration of serial PERMPs)
- Visit 5 (Administration of serial PERMPs)

4.2.10.1 Screening

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 (ICF). Potential subjects who give their informed consent will undergo a screening period (up to 6 weeks) to determine eligibility prior to Baseline.

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

- Subject's informed consent
- Review of inclusion/exclusion criteria
- Review of medical history
- Review of medication history including prior and concomitant medications
- Demographics (i.e., sex, age, race, and ethnicity)
- Physical examination
- Body weight and height
- M.I.N.I. 7.0.2
- AISRS
- ACDS
- CGI-S
- "Baseline" C-SSRS
- PERMP placement test (may be performed at Baseline)
- Vital Signs: Blood pressure (BP) and pulse (average of triplicate measurements), respiratory rate (RR), and temperature (T).
- Resting 12-lead ECG
- AE assessment
- Laboratory tests (see Table 2)

Table 2: Laboratory Tests at Screening

Biochemistry	Non-fasting random serum glucose
	Total bilirubin
	Blood urea nitrogen (BUN)
	Creatinine with estimated glomerular filtration rate (eGFR)
	Alkaline phosphatase
	Calcium

	Lactate dehydrogenase (LD)
	Aspartate aminotransferase [AST (SGOT)]
	Alanine aminotransferase [ALT (SGPT)]
	Serum electrolytes (sodium, potassium, and chloride)
	Gamma glutamyl transpeptidase (GGT)
Hematology	Complete blood count (CBC) with differential: • White blood cell count (WBC) with differential • Hemoglobin • Hematocrit • Red blood cell count (RBC) to include indices
	Platelet count
Serology	HIV
	Hepatitis C antibody Hepatitis B surface antigen
Immunohematology:	Serum hCG (females only)
Urinalysis	Specific gravity
	Urine color
	Appearance
	Bilirubin
	pH
	Leukocytes
	Nitrites
	Protein
	Glucose
	Ketones
	Blood
	Microscopic examination ***Note:*** *Microscopic examination will only be performed when any of the following urinalysis tests are reported abnormal (i.e., outside of normal ranges): leukocyte, nitrite, protein, and/or blood. The microscopic examination will be conducted on the same urine sample as the abnormal urinalysis test.*
Drugs of Abuse:	Amphetamines
	Barbiturates
	Benzodiazepines
	Cannabinoids
	Cocaine
	Methadone
	Opiates
	Phencyclidine
	Tricyclic antidepressants

4.2.10.2 Baseline (Day -1)

Once the subject is determined to be initially eligible at Screening, Baseline evaluations will be performed. If the subject continues to meet eligibility criteria at Baseline, the subject may be enrolled into the study and randomized to start the DB titration phase.

AMPH ER TAB (or matching placebo) will be dispensed to enrolled subjects. The starting dose of AMPH ER TAB (or matching placebo) will be 5 mg in the morning before 10 am, with or without food, swallowed whole or chewed.

The following assessments will occur at the Baseline Visit:

- Review of inclusion/exclusion criteria
- M.I.N.I. 7.0.2 (if not performed at Screening)
- PERMP placement test (if not performed during Screening)
- PERMP practice before and after safety and efficacy assessments
- Urine pregnancy test (females of childbearing potential only)
- "Since Last Visit" C-SSRS
- AISRS
- ACDS (if subject did not meet eligibility criteria at Screening)
- CGI-S
- DSST
- Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events
- Vital Signs: BP and pulse (average of triplicate measurements)
- Body weight
- AE assessment
- Concomitant medications assessment
- DB AMPH ER TAB 5 mg or matching placebo dispensing, accountability, and subject training regarding investigational product
- Drugs of Abuse Screening Test (see Table 3)

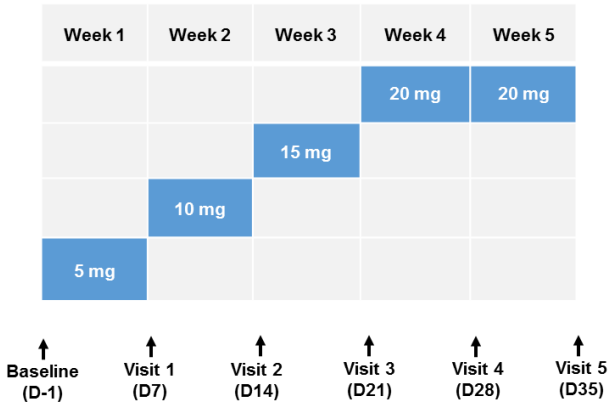
Table 3: Drugs of Abuse Screening Test at Baseline

Drugs of Abuse:	Amphetamines
	Barbiturates
	Benzodiazepines
	Cannabinoids
	Cocaine
	Methadone
	Opiates
	Phencyclidine
	Tricyclic antidepressants

4.2.10.3 Visits 1 (Day 7) to 3 (Day 21), Double-Blinded Titration

During Visits 1 to 3, enrolled subjects will continue to receive AMPH ER TAB or matching placebo as described in Figure 2 Dose Titration. Subjects will be titrated up by 5 mg increments each week. After Visit 3 subjects will receive a final dose of 20 mg for 14 (± 3) days prior to Visit 5. Subjects who cannot tolerate the study drug will be discontinued from the study.

Figure 2: Dose Titration



The following assessments will be performed at each visit during Visit 1 to 3:

- Blood pressure and pulse (average of triplicate measurements)
- Body weight
- PERMP practice before and after efficacy and safety assessments
- AISRS
- CGI-S
- "Since Last Visit" C-SSRS
- Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events
- AE assessment
- Concomitant medications assessment
- DB AMPH ER TAB (10 mg after Visit 1, 15 mg after Visit 2 and 20 mg after Visit 3) or matching placebo dispensing, accountability, and subject training regarding Investigational Drug.

4.2.10.4 Visit 4 (Day 28) Abbreviated administration of serial PERMPs

The following assessments will be performed at Visit 4:

- Blood pressure and pulse (average of triplicate measurements) at pre-dose and ~3 hours post-dose
- Body weight
- Abbreviated administration of serial PERMPS at pre-dose, 0.5, 1, 2 and 4 hours post-dose. Pre-dose PERMP will be administered approximately 30 minutes prior to dosing, followed by on-site administration of AMPH ER TAB 20 mg or matching placebo by the clinic staff.

- AISRS
- CGI-S
- "Since Last Visit" C-SSRS
- Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events
- AE assessment
- Concomitant medications assessment
- DB AMPH ER TAB 20 mg or matching placebo dispensing, accountability, and subject training regarding investigational drug.

4.2.10.5 Visit 5 (Day 35) Administration of serial PERMPs

The following activities will be performed during Visit 5:

- Administration of serial PERMPs at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose
- Physical examination
- Blood pressure and pulse (average of triplicate measurements) at pre-dose and ~3 hours post-dose
- Body weight
- On-site drug administration of AMPH ER TAB 20 mg or matching placebo
- AE assessment
- Concomitant medications assessment
- Study drug accountability and drug reconciliation

The following activities will be performed at or within 2 days of Visit 5:

- AISRS
- CGI-S
- DSST
- "Since Last Visit" C-SSRS
- Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events
- Resting 12-lead ECG
- Laboratory tests (see Table 4)

Table 4 Laboratory Tests at Visit 5

Biochemistry	Non-fasting random serum glucose
	Total bilirubin
	Blood urea nitrogen (BUN)
	Creatinine with estimated glomerular filtration rate (eGFR)

	Alkaline phosphatase
	Calcium
	Lactate dehydrogenase (LD)
	Aspartate aminotransferase [AST (SGOT)]
	Alanine aminotransferase [ALT (SGPT)]
	Serum electrolytes (sodium, potassium, and chloride)
	Gamma glutamyl transpeptidase (GGT)
Hematology	Complete blood count (CBC) with differential: • White blood cell count (WBC) with differential • Hemoglobin • Hematocrit • Red blood cell count (RBC) to include indices
	Platelet count
Immunohematology:	Urine hCG (females only)
Urinalysis	Specific gravity
	Urine color
	Appearance
	Bilirubin
	pH
	Leukocytes
	Nitrites
	Protein
	Glucose
	Ketones
	Blood
	Microscopic examination ***Note:*** *microscopic examination will only be performed when any of the following urinalysis tests are reported abnormal (i.e., outside of normal ranges): leukocyte, nitrite, protein, and/or blood. The microscopic examination will be conducted on the same urine sample as the abnormal urinalysis test.*

- Drug of Abuse Screening Test (see Table 5)

Table 5 Drugs of Abuse Screening Test at Visit 5

Drugs of Abuse:	Barbiturates
	Benzodiazepines
	Cannabinoids
	Cocaine
	Methadone
	Opiates
	Phencyclidine
	Tricyclic antidepressants

For all activities performed, the results are to be recorded in the eCRF.

4.2.10.6 Early Termination Visit

The following activities may be done for subjects that withdraw prior to completion of Study Visit 5 (i.e., terminate early):

- Physical examination
- Body weight

- BP and pulse (average of triplicate measurements)
- AE assessment
- Concomitant medications assessment
- "Since Last Visit" C-SSRS
- Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events
- AISRS
- CGI-S
- DSST
- Study drug accountability and reconciliation
- A urine pregnancy test (for females of child-bearing potential only) may be performed in the event of a suspected pregnancy per Investigator's clinical judgment
- Any other assessments as determined by the Investigator

For all activities performed, the results are to be recorded in the eCRF.

5 INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

5.1 Investigational Drug Dose Regimen

DB AMPH ER TAB or matching placebo will be dispensed to enrolled subjects. Subjects will be instructed to take AMPH ER TAB in the morning before 10 am, with or without food, swallowed whole or chewed. The starting dose of AMPH ER TAB (or placebo) after Baseline will be 5 mg. Subjects will then be titrated up by 5 mg each week. After Visit 3 subjects will receive a final dose of 20 mg for 14 (± 3) days prior to Visit 5. Subjects who cannot tolerate the study drug will be discontinued from the study.

5.2 Investigational Drug Packaging, Labeling and Dispensing

AMPH ER TAB or matching placebo will be provided in blinded packaging at Baseline and Visits 1 to 4. AMPH ER TAB and placebo will have identical physical characteristics and matching flavor.

All investigational products used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of Tris Pharma or those of its designee, Current Good Manufacturing Practices (cGMP) guidelines, International Conference for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and applicable regulations.

5.3 Investigational Drug Storage

The study drug should be stored between 15°C to 30°C (59°F to 86°F) at the study center in a secure, locked cabinet with limited access. When dispensed, the subjects will be instructed to store the drug at ambient temperature in a cool, dry place and out of reach of children.

5.4 Drug Administration

The study drug will be administered orally once daily before 10 am with or without food. Subjects will be instructed to take each study drug dose by swallowing or chewing. Drug administration for Visits 4 and 5 will occur on-site.

5.5 Investigational Drug Accountability

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

Drug accountability will be performed at each study visit starting with Baseline. Subjects will be provided with a new bottle containing 10 tablets at each visit (Baseline and Visits 1 to 4). Containers including the remaining study drug samples should be returned to the site at each subsequent visit. Remaining drug product samples and empty containers will be retained at the site for Study Monitor and/or Sponsor verification. All drug product samples should be stored at the study site until further instruction from the Sponsor.

5.6 Investigational Drug Handling and Disposal

All study drug samples will be accounted for on drug inventory records (including records of study drug sent to the Investigator and records generated at the investigational site). The Sponsor and/or its designate will review inventory forms during the study and at the conclusion of the study. The Investigator will sign the drug inventory record after resolving any questions resulting from the Sponsor and/or its designee's review. The Investigator must retain a copy of all drug inventory records.

All remaining used and unused study drug must be retained until final instructions are given by the Sponsor.

Tris Pharma will provide detailed drug return instructions to the study site. All post-treatment handling and disposal of study drug will be in accordance with GCP and cGMP guidelines and federal and local regulations.

6 SUBJECT COMPLIANCE

6.1 Concomitant Medication and/or Therapy

Concomitant medications information will be collected beginning at Screening and will continue during all study visits or Early Termination (EOT) visit, if applicable.

6.2 Prohibited Concomitant Medications

Psychotropic medications are not allowed during the study except for stimulants (other than study drug), which must be discontinued within 7 days of Baseline. No anticonvulsant, antidepressant, or antipsychotic medications are permitted during the study. Melatonin is permitted. Prohibited concomitant medications may be resumed 1 day after Study Visit 4 (or EOT).

6.2.1 Prohibited Concomitant Medications

Any stimulant (e.g., methylphenidate, dexmethylphenidate, amphetamine, and dextroamphetamine) should be discontinued 7 days prior to Baseline. The following medications are prohibited during the study:

Selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine)
Serotonin and norepinephrine reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, venlafaxine – with the exception of fluoxetine which is restricted for 30 days prior to Baseline)
MAOIs
Mood stabilizers (e.g., lithium, valproate, quetiapine)
Antipsychotics (e.g., risperidone, olanzapine)
Anticonvulsants (e.g., phenobarbital, phenytoin, primidone)
Sedative hypnotics, except melatonin
Anticoagulants
Halogenated anesthetics
Tricyclic antidepressants
Atomoxetine
Guanfacine
Clonidine
CYP2D6 inhibitors (e.g., paroxetine and fluoxetine, quinidine, ritonavir)
Fentanyl, tramadol, tryptophan, buspirone, St. John's Wort
Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid)
Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts
Decongestants (e.g. oxymetazoline, phenylephrine, pseudoephedrine)
Sedating antihistamines (e.g. alimemazine, chlorphenamine, clemastine, cyproheptadine, hydroxyzine, promethazine)

Acetaminophen is permitted for control of fever or pain if needed. Short courses of prescription and non-prescription medications needed for treatment of acute illnesses such as the common cold, viral illnesses, and ear infections are permitted as long as these do not contain medications listed above. Ongoing antihypertensive treatment will be assessed by the Investigator and the Sponsor.

Alcohol consumption will be restricted form Baseline to 24 hours after Visit 5.

All concomitant medications must be recorded on the Concomitant Medication CRF.

The Investigator should contact the Medical Monitor for a written Note to File or Memo to File for evidence that the Sponsor is aware of a chronic or acute medication and a judgment on whether the subject may continue in the study.

6.3 Treatment Compliance

Subject training at Baseline and subsequent ongoing retraining regarding proper dosing of study drug will occur to ensure subject compliance. Subjects must be instructed to return to every visit any unused study drug and/or the empty bottle. Starting with Visit 1, study staff will assess compliance by inspecting returned study drug bottles at every study visit to confirm that the subject is taking study drug according to the protocol. Drug accountability per subject will be recorded on drug accountability logs. If the subject forgets to bring the bottle to the visit, the visual inspection will occur when the bottle is returned.

6.3.1 Acceptable Compliance

Acceptable compliance is defined as 80% or higher which is inclusive.

If compliance between subsequent scheduled visits is outside this acceptable range and/or cannot be determined (when, for example, the subject did not return unused study drug), the Investigator or designee will determine subject's continued participation, after consultation with the Clinical Monitor and the Sponsor.

7 RANDOMIZATION AND BLINDING PROCEDURES

Enrollment will occur after all Screening procedures have been performed and eligibility for the study is confirmed at Baseline. After Baseline, subjects will enter a 4-week randomized, DB, placebo-controlled phase. Subjects will be randomized at Baseline to take DB AMPH ER TAB (or matching placebo) orally once daily.

All study drug product samples will be supplied in identical containers and will be similar in physical characteristics (color, smell, flavor, and appearance), thereby enabling DB conditions.

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 Sponsor prior to unblinding. For emergency unblinding, study personnel will use the IWRS unblinding module.

Table 6 Sponsor's Contact Information for Unblinding Procedures

Contact	Phone number	Fax number
Tris Pharma, Inc Cary Sax Director, Regulatory Affairs csax@trispharma.com	Direct # 732-823-4690	NA

A subsequent written report, including all pertinent details, must be submitted to the Sponsor within 24 hours of the unblinding. Whenever possible, the blind of the subject should be maintained.

If Investigator or site personnel or subject unblinded, the subject must be withdrawn from the study, and procedures accompanying withdrawal are to be performed.

8 ADVERSE AND SERIOUS ADVERSE EVENTS

This section defines AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312, *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, *and ICH Guideline E6(R2): Good Clinical Practice.*

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study, when there is a safety evaluation, the Investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

8.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, whether or not the event has a causal relationship with this treatment.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE.

Examples of an AE include the following:

- significant or unexpected worsening or exacerbation of the condition or indication under study, taking into consideration the daily fluctuation of symptoms of ADHD.
- exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (e.g., abnormal physical examination finding)
- signs, symptoms, or clinical sequelae of a suspected interaction
- signs, symptoms, or clinical sequelae of a suspected overdose of the study medication or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless non-serious or serious sequelae occur)

The following examples are not considered AEs:

- medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen
- the disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition

8.2 Definition of a Serious Adverse Event (SAE)

An SAE is defined as any event that meets the following criteria:

- It results in death
- It is life-threatening (i.e., presents an immediate risk of death from the event as it occurred) (This criterion does not mean that the AE hypothetically might have caused death if it were more severe)
- It results in persistent or substantial disability or incapacitation (This criterion is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle)
- It results in hospitalization
- It results in prolongation of an existing hospitalization
- It is a congenital anomaly or birth defect
- It requires medical or surgical intervention to prevent any of the above outcomes
- Other medically important condition

  (Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency.)

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline does not meet the definition of an SAE.

Admission to a hospital or prolongation of a hospitalization for social or convenience reasons (e.g., cosmetic surgery) not associated with the occurrence of an AE does not meet the definition of an SAE.

8.2.1 Serious Adverse Events That Occur Before Administration of Study Medication

Before administration of study medication, only SAEs assessed by the Investigator as related to study participation (e.g., related to study procedures or a change in existing therapy) will be transcribed onto the SAE reporting form and reported to the Sponsor via Premier Research Pharmacovigilance

8.2.2 Serious Adverse Events That Occur After Study Completion

If the Investigator becomes aware of an SAE or death that occurs in a subject within 30 days after Visit 4and that Investigator considers the event to be related to the study medication, the Investigator is obligated to report the SAE to the Sponsor.

8.3 Collecting, Recording and Evaluating Adverse Events and Serious Adverse Events

The AE reporting period for this study begins at Screening and ends at Visit 4. All AEs that occur in trial subjects during this reporting period must be reported, without consideration to drug relatedness. In addition, any known AE that occurs subsequent to the AE reporting period that the investigator assesses as related to the study medication should also be reported as an adverse event.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE. AEs will be collected from the point the ICF is signed through EOT or Early Termination Visit.

Both total and treatment-emergent AEs will be reported. Treatment-emergent AEs are defined as those that occur after dosing of study medication until EOT or Early Termination Visit.

8.3.1 Assessment of Adverse Events and Serious Adverse Events

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

* “How are you feeling?”

* “Have you experienced any issues since your last visit?”

* “Have you taken any new medications since your last visit?”

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

8.3.2 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded on the CRF should be assigned to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe**: An event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. *Severity* is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as *serious,* which is based on the subject’s or event’s outcome or on action criteria usually associated with events that pose a threat to a subject’s life or functioning (see Section 8.2).

8.3.3 Assessment of Causality

The Investigator is obligated to use his or her clinical judgment to assess the relationship between the study medication and the occurrence of each AE or SAE. The Investigator will assess the relationship to the study medication by using the following criteria:

- **Definitely Related**: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely
- **Probably Related**: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive
- **Possibly Related**: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause; dechallenge is positive
- **Not Related**: The subject did not receive the study drug **OR** the AE has no temporal relationship to study drug **OR** the AE has a much more likely alternate etiology **OR** the AE is due to an underlying or concurrent illness or effect of another drug

Even in situations in which minimal information is available for the initial SAE report, it is important that the Investigator always makes an assessment of causality for every event before transmitting the SAE reporting form and AE CRF page(s) to the Sponsor. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality in light of follow-up information and amend the SAE reporting form and AE CRF page(s) accordingly.

8.3.4 Assessment of Outcome

All SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The Investigator will assess the outcome of the event by using the following terms:

- **Resolved**: The event resolved or the subject recovered without sequelae. An event (either serious or non-serious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequelae), an appendectomy (a scar is not a sequelae), a post-operative wound infection, or an upper respiratory tract infection
- **Resolved with sequelae**: The event has at least 1 secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function
- **Resolving**
- **Not resolved**: At the end of the study, an event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown.

- **Unknown**: The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown
- **Death**

8.4 Documentation

All AEs that occur within the period of observation for the study must be documented in the CRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken; may consist of:
    - **Dose increased**: An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount.
    - **Dose not changed**: An indication that a medication schedule was maintained.
    - Dose reduced: An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
    - **Drug interrupted:** An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
    - **Drug withdrawn**: An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
    - **Not applicable:** Determination of a value is not relevant in the current context.
    - **Unknown**: Not known, not observed, not recorded, or refused.
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

8.5 Follow-up of Adverse Events and Serious Adverse Events

Non-serious AEs will not be followed after the last scheduled study visit.

SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. The Investigator will make a reasonable attempt to obtain follow-up information and provide it to the Sponsor via Premier Research Pharmacovigilance. This includes results of any additional laboratory tests or investigations or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.

New or updated information will be recorded on the originally completed SAE reporting form and CRF pages, with all changes signed and dated by the Investigator. The updated SAE reporting form and CRF pages should be resubmitted to the Sponsor via Premier Research Pharmacovigilance within the time frames outlined in Section 8.6. Investigators with subjects with unresolved SAEs at the time that the electronic database is to be closed will be informed and instructed how to make subsequent updates on the SAE to the Sponsor. The database will be locked and the data analyzed if unresolved SAEs remain. SAE updates will be reported to the Sponsor, to Regulatory Authorities, and IRBs within the timelines required by applicable regulations. All updates will also be filed in the Trial Master File retained by the Sponsor.

8.6 Prompt Reporting of Serious Adverse Events

Once the Investigator determines that an event meets the protocol definition of an SAE, he or she must notify the CRO within 24 hours, including weekends and holidays.

ANY SAE OR ANY OUTCOME OF DEATH DUE TO ANY CAUSE WHICH OCCURS DURING THE COURSE OF THIS STUDY, REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (WITHIN 24 HOURS).

Complete the SAE Reporting Form and forward by e-mail or fax to Premier Research Pharmacovigilance:

Table 7 Contact Information for SAE Reporting

What	Email	Phone/ Fax
24 Hour US Contact	GlobalPV-US@premier-research.com	Fax: +1 215 972 8765

E-mail transmission is the preferred method to transmit SAE information. In rare circumstances, and in the absence of e-mail capacity, notification by fax is acceptable

If the Investigator does not have all information regarding an SAE, he or she must not wait to receive additional information before notifying the CRO of the event. The form must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the CRO by using the same procedure and timelines as for an initial report.

Within 24 hours after a SAE detection, observation, or report of occurrence (regardless of the relationship to test article), the investigator/qualified designee will complete a paper SAE Report Form with required information regarding the SAE and submit the completed form to Premier Research Pharmacovigilance. The data will also be entered into the appropriate module of the electronic data capture (EDC) as soon as possible after the paper form is sent to Premier Research Pharmacovigilance.

These SAE reports must contain the following information:

1. Study name/number
2. Study drug

3. Investigator details (name, phone, fax, e-mail)
4. Subject number
5. Subject demographics
6. Clinical event
7. Description
    a. Date of onset
    b. Treatment (drug, dose, dosage form)
    c. AE relationship to study drug
    d. Action taken regarding study drug in direct relationship to the AE
    e. Criteria for "Serious" applicable to the AE
8. Cause of death (whether or not the death was related to study drug)
9. Autopsy findings (if available)
10. Date of firs dose of Investigational Product
11. Date of last dose of Investigational Product, if applicable

Any SAE that occurs during the study should be recorded by each clinical site and reported to the Sponsor Premier Research Pharmacovigilance.

SAEs considered definitely, probably, or possibly related to study drug shall also be classified by the Sponsor as being "expected" or "unexpected." An unexpected event is one that is not listed in the Investigator's Brochure.

The person responsible for the study shall ensure the study has been carried out in accordance with local pharmacovigilance regulations. All serious events reporting by Sponsor will adhere to 21 CFR 312.32 for IND drugs (7-day or 15-day alerts). Unexpected fatal or life-threatening SAEs considered related to the study drug should be reported to the FDA by the Sponsor with an Investigational New Drug (IND) Safety Report within 7 days. The Institutional Review Board (IRB) will be notified of the alert reports per FDA regulations.

8.7 Regulatory Reporting Requirements for Serious Adverse Events

The Investigator must promptly report all SAEs to the CRO or designee in accordance with the procedures detailed in Section 8.6, "Prompt Reporting of Serious Adverse Events".

The Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB. The Sponsor is responsible for reporting to Regulatory Authorities.

8.7.1 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject, or a male subject's partner become pregnant or be suspected of being pregnant while participating in this study, the event must be reported to the Sponsor upon receipt of information by the study staff. While the pregnancy itself is not considered to be an AE or a SAE, any pregnancy

complications will be recorded as AEs or SAEs (if applicable). Pregnancy must be reported within 24 hours from first knowledge to the Sponsor via Premier Research Pharmacovigilance in writing via the Pregnancy Data Collection Form. This form shall be forwarded by e-mail or fax to the contacts details in Section 8.6.

Any pregnancy will be followed through to delivery for the observation of any SAEs including congenital abnormalities. Fatalities and spontaneous abortions must be reported as SAEs.

8.7.2 Overdose

The maximal dose of Investigational Product (20 mg) should not be exceeded during the study. Overdose that occurs during the study will be treated and documented as an AE/UAE/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be documented in the CRF. If the overdose does result in an SAE, it should be documented in the CRF and reported via a completed the SAE Reporting Form which is forwarded by e-mail or fax to Premier Research Pharmacovigilance The information contained therein should include study site identification, reporter identification, subject identification, Investigational Product, dose, action taken (e.g., administration of antidote <if available> or supportive measures or therapy), and any comments.

9 STATISTICAL CONSIDERATIONS

This is a phase 3 randomized, double-blind (DB), placebo-controlled, parallel, study to assess the efficacy and safety of AMPH ER TAB compared to placebo for the treatment of ADHD in adults aged 18 to 60 years. The objective of the statistical analysis will be to evaluate the efficacy and safety of AMPH ER TAB compared to placebo in adult patients with ADHD aged 18 to 60 years.

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 0.05 significance level.
A detailed statistical analysis plan (SAP) will be written and finalized prior to unblinding of the data.

9.1 Power and Sample Size Determination

Assuming an effect size of 0.80 of the primary efficacy endpoint (PERMP-T score averaged over all post-dose time points assessed at Visit 5) between AMPH ER Tabs and placebo and approximately 92 completers, this study will have at least 93% power at the level of 0.05 (2-sided). To allow for an estimated 15% potential dropout rate, this study plans to enroll approximately 108 subjects to ensure that at least 92 complete. The study will be conducted in approximately 6 cohorts of 18 subjects because subjects will need to be enrolled in cohorts to facilitate the administration of serial PERMPs at Visits 5. An additional cohort of up to 18 subjects may be added to ensure at least 92 subjects complete the study if there are circumstances in which any of the cohorts are unable to enroll 18 subjects, or if the dropout rate is higher than expected (>15%) thereby having less than 92 completers to ensure sufficient statistical power.

The assumed effect size of 0.80 (expected treatment difference of 18 in average PERMP-T score divided by between-subject square root mean square error of 21.75) is based on differences measured between active and placebo in previous laboratory school studies conducted with similar drug formulations.

9.2 Analysis Populations

The analysis populations are defined as follows:

- **Safety Population (SAF)**: The safety population is defined as all enrolled subjects who received at least one dose of study drug, with treatment assignment based on the actual treatment received.
- **Randomized Population (RAND)**: The randomized population is defined as all randomized subjects, with treatment assignment based on the randomized treatment (regardless of actual treatment received).
- **Intent-To-Treat Population (ITT)**: The ITT population is defined as all randomized subjects who received at least one dose of study drug treatment, with treatment assignment based on the randomized treatment (regardless of actual treatment received).
- **Modified Intent-To-Treat Population (mITT)**: The mITT population is defined as all subjects who are in the ITT population and have at least one PERMP-T score at Visit 5.

The primary efficacy analysis and key secondary efficacy analysis will be performed on the mITT population. Analysis of additional secondary endpoints will be performed for ITT population.

The safety analyses will be performed on the safety populations.

Deviations from the original statistical plan as planned in this protocol will be reported and justified in the SAP and clinical study report (CSR) as appropriate.

9.3 Efficacy and Safety Analyses

9.3.1 Disposition and Withdrawals

The number of subjects randomized, completing, and withdrawing, along with the reasons for withdrawal, will be tabulated. Additionally, the number of subjects in each analysis population will be reported.

9.3.2 Protocol Deviations

A by-subject listing of all protocol deviations will be reported.

9.3.3 Background and Demographic Characteristics

Baseline demographic variables will be summarized and presented by a subject listing. Demographic information will be presented for all analyses populations as defined in Section 9.2.

9.3.4 Concomitant Medications and Concomitant Therapies

Concomitant medications and therapies will be summarized by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) class level 4 and preferred term. Concomitant medications will also be listed by subject.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analysis

The primary efficacy endpoint and estimand are defined in Section 3.2.1.

PERMP-T scores at all post-dose time points (0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose) at visit 5 will be assessed using a linear MMRM analysis. This is a restricted maximum likelihood (REML)-based analysis implemented using SAS PROC MIXED. The model will include treatment, time and treatment by time as fixed effects and subject as a random effect. Pre-dose PERMP-T score will be included as a covariate. The difference between AMPH ER TAB and placebo will be assessed at the alpha = 0.05 level of significance. The covariance structure used in the final MMRM model will be the one that has the lowest Akaike Information Criterion (AIC) among the following selections: SP(POW), unstructured, compound symmetry (CS), heterogeneous CS or heterogeneous Toeplitz. Kenwood-Roger correction will be used to estimate denominator degrees of freedom. The treatment effect is estimated by the overall adjusted least square mean difference between two treatment groups. 95% CI for the adjusted least square mean will be constructed and p-value for the treatment comparison will also be provided.

The primary efficacy analysis will be conducted on the mITT population.

For the primary efficacy analysis, the MMRM model will be fit to the observed data with missing at random assumption. The rate of missing PERMP-T for at least one post-dose time point on will be calculated and summary (number and percentage) of subjects discontinued prior to Visit 5 by the

dose level (5, 10, 15, 20 mg) prior to discontinuation will be summarized. Sensitivity analysis will be performed using Multiple Imputation approach with missing not at random assumption. In this analysis, the mean difference between the (unobserved) missing values and observed values (refer to as shift) will be assumed to vary independently for the different treatment groups. More details of this procedure will be provided in SAP.

9.3.5.2 Secondary Efficacy Analyses

Key secondary efficacy outcomes as determined by the comparison of each PERMP-T score at each time point (0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose) with pre-dose PERMP-T scores at Visit 5 are:

- Onset of clinical effect
- Duration of clinical effect

The key secondary variables of onset and duration of efficacy (clinical effect) of APMH ER TAB versus placebo using the comparison of each PERMP-T ((attempted + correct) score at each time point will be tested by the same method as the primary efficacy endpoint analyses implementing a linear MMRM model.

Onset of clinical effect is defined as the first time point post-dose when treatment effect is significant while the duration of clinical effect is defined as the time between last time point to the first time point post-dose with significant treatment effect.

The key secondary efficacy analysis will be conducted on the mITT population.

The key secondary efficacy endpoints (in the order of statistical analysis/gating) include:

- PERMP-T scores at 4, 2, 8, 10, 12, 1, 0.5, 13, and 14 hours post-dose

Descriptive statistics for the PERMP-T scores will be calculated at each time point and will be presented for each treatment as well for the differences between the treatments (AMPH ER TAB-placebo). In addition, these variables will be analyzed by the same method as the primary efficacy endpoint analyses implementing a linear MMRM model as described in Section 9.3.5.1 for the primary efficacy variable.

Additional secondary efficacy endpoints will include

- Change from Baseline in CGI-S at each post-baseline visit
- Change from Baseline in AISRS scores at each post-baseline visit
- Change from Baseline in DSST at Visit 5

Analysis of additional secondary endpoints will be performed for ITT population.

Descriptive statistics for the CGI-S, AISRS will be presented for each visit (Baseline and Visits 1 to 5). In addition, the change from Baseline in CGI-S, AISRS and DSST will be summarized.

For the AISRS, the proportion of responders (defined as a subject who has a change from Baseline 50% or greater in the AISRS) will also be presented.

9.3.6 Safety Analyses

Safety assessments will include TEAEs, physical examination, vital signs, body weight, Columbia Suicide Severity Rating Scale (C-SSRS), laboratory results, Electrocardiograms (ECG), vital signs and body weight, and direct questioning to assess for sleep, appetite, mood and psychotic events.

All safety data will be analyzed descriptively by treatment group.

The frequency of subjects reporting AEs will be summarized within each system organ class and preferred term.

9.3.6.1 Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Treatment-emergent AEs, any AEs recorded during the study at least one dose of study medication, will be summarized and categorized by severity and relationship to the investigational drug. If a subject has more than one occurrence of the same AE, he/she will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures or investigational drug, will be indicated in cases of multiple occurrences of the same AE. Serious adverse events and AEs of special interest, which will be defined in the SAP, will also be summarized separately. All AEs will be presented in a listing. Additionally, listings of SAEs and AEs leading to discontinuation will be generated. All SAEs will be evaluated to determine whether they are Unexpected Adverse Reactions.

9.3.6.2 Columbia Suicide Severity Rating Scale (C-SSRS)

The frequency of suicidality using the C-SSRS will be summarized by treatment group for the number of subjects reporting at least 1 occurrence of suicidal ideation or behavior, the number of subjects reporting any type of suicidal behavior, and the number of subjects reporting any type of suicidal ideation.

9.3.6.3 Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events

Occurrences related to sleep, appetite, mood, and psychotic events will be summarized descriptively by treatment and time point.

9.3.6.4 Clinical Laboratory Evaluations

Laboratory test results will be summarized descriptively by treatment and time point as both observed values and change from baseline values.

The number of subjects with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each clinical laboratory analyte by treatment group (shift table).

Laboratory values that are outside the normal range will be flagged in the data listings.

9.3.6.5 Vital Signs and Body Weight

Descriptive summaries of actual values and changes from Baseline will be calculated for vital signs and weight.

9.3.6.6 Electrocardiograms (ECG)

The number and percentage of subjects with normal and abnormal ECG results will be summarized for the Safety Population by study phase and treatment group.

9.3.7 Other Statistical Considerations

9.3.7.1 Significance Levels

The type I error significance level for each set of study analyses as applicable will be set at alpha = 0.05.

To preserve the family-wise error rate of 0.05, a gatekeeping testing procedure will be implemented for primary/secondary efficacy endpoints in the following order:

- PERMP-T scores over all post-dose time points assessed at Visit 5
- PERMP-T scores at 4, 2, 8, 10, 12, 1, 0.5, 13 and 14 hours post-dose

The above will test in sequence whether a significant treatment effect is present using the models previously specified. If a significant effect is noticed, the following test will then be examined until all endpoints are exhausted or failure to reject the null hypothesis is met at alpha = 0.05.

9.3.7.2 Missing Data

No imputation of missing PERMP scores will be done for the primary efficacy analysis. To evaluate the sensitivity of the primary analysis results to the use or non-use of imputation, analyses using multiple imputation methods will be conducted as mentioned in Section 9.3.5.1. Additional details will be described in the SAP.

9.3.8 Visit Windows

All data collected will be displayed and analyzed according to the actual visit data in the eCRF. Study visits may occur within a ± 3-day window of the weekly scheduled visit and ensuring that the maximum length of exposure to the Investigational Product prior to Visit 5 shall be 35 (± 3) days. The maximum dose of AMPH ER TAB 20 mg (or matching placebo) will be administered for 14 (± 3) days prior to visit 5.

Assessments taken outside of windows described in the protocol will be displayed according to the eCRF assessment recorded by the Investigator.

10 DIRECT ACCESS TO PROCEDURAL DOCUMENTS

10.1 Study Monitoring

According to Good Clinical Practices (GCP) guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The contract research organization (CRO) is responsible for assigning the study monitor(s) to this study, with prior approval from the Sponsor. The study monitors' duties are to aid the Investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the Investigator of the regulatory necessity for trial-related monitoring, audits, IRB review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the Investigator all regulations applicable to the clinical evaluation of an investigational drug as documented in ICH guidelines.

It is the study monitors' responsibility to inspect the eCRFs throughout the study to protect the rights of the subjects; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details may be outlined in the study monitoring plan.

10.2 Source Documents

Tris Pharma requires that the Investigator prepare and maintain adequate and accurate records for each subject treated with the investigational drug. Source documents such as any hospital, clinic, or office charts and the signed ICFs are to be included in the Investigator's files with the subject's study records.

Data will be captured electronically. Study site personnel will record eCRF data from source documents. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

10.3 Data Collection and Management

This study will use electronic data collection techniques to collect data directly from the investigational site using eCRFs. The data will be stored centrally in a fully validated clinical database compliant with FDA regulations on electronic data integrity. The Investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform 100% source document verification to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

At intervals throughout the study and upon completion, data will be exported from the database into SAS datasets.

Data management will be coordinated by the data managers of the designated CRO in accordance with their SOPs for data management and a formal study data management plan. The data managers will provide a quality control statement following database lock.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using World Health Organization – Drug Reference List.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed, and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from Tris Pharma (or a qualified delegate), who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

12 ETHICS

12.1 Ethics Review

This research will be carried out in accordance with GCP as set out by the ICH Guidance for Industry, E6(R2) GCP: Good Clinical Practice; the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312); the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, October 2013); and in accordance with all national, state, and local laws and regulations.

12.2 Ethics Committees

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the site's ICFs, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB. The Investigator agrees to allow the IRB direct access to all relevant documents. The IRB must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the Investigator with relevant documents or data needed for IRB review and approval of the study. Before investigational products can be shipped to the site, the Sponsor must receive copies of the IRB approval, the approved ICF, and any other information that the IRB has approved for presentation to potential subjects.

If the protocol, the ICFs, or any other information that the IRB has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring that the IRB reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF, including obtaining IRB approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The Investigator must promptly forward to the Sponsor copies of the IRB approval of the amended ICF or other information and the approved amended ICF or other information. IRB approval of the consent forms must be obtained in addition to the approval given for the clinical study.

12.3 General Considerations

The Investigator must conduct the study in accordance with this protocol and ICH GCP guidelines which have their origins in the Declaration of Helsinki. The Investigator and Tris Pharma will sign the protocol and study contract to confirm agreement. The Investigator will not implement any amendment (deviation or changes of the protocol) without agreement by Tris Pharma and the IRB approval/information, except where necessary to eliminate immediate hazards to study subjects or when changes involve only logistical or administrative aspects of the study.

When any new and important information that may be relevant to the subject's consent is obtained, the Investigator and Tris Pharma will consult with each other on how to deal with the information. When Tris Pharma and a responsible Investigator judge it necessary, the Investigator must immediately provide the subjects with such information, revise the written information and other explanatory documents based on the new information, and obtain approval from the IRB(s). In this instance, the Investigator should also immediately inform subjects currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision.

12.4 Informed Consent Form (ICF)

The Sponsor will provide Investigators with a sample ICF for this study. Investigators are encouraged to use the sample form; however, they may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final ICF must be accepted by the Sponsor and approved by the IRB. Investigators must provide the Sponsor with an unsigned copy of the final ICF before and after it is approved by the IRB. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the ICF, the Sponsor will provide Investigators with a revised ICF. The IRB must provide written approval of any revisions to the ICF in advance of its use.

Investigators must provide subjects with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, and possible risks.

Before written informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject.

Before a subject undergoes procedures specific to the protocol, the ICF must be signed and dated by the subject and any other signatories as required by the IRB.

After all required signatures have been obtained, a copy of the signed ICF should be provided to the subject, and the original must be kept on file at the site and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

12.5 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. Each subject will be asked to complete a form allowing the Investigator to notify the subject's primary health care provider of his/her participation in this study.

12.6 Publications of the Clinical Study

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR § 50.25(c). The results of and data from this study belong to Tris Pharma. Investigators may not publish on the results from the study (including data specifically from their site) without prior written consent from Tris Pharma.

12.7 Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Tris Pharma after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Tris Pharma. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Tris Pharma. IRB approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor and the regulatory authorities (e.g., FDA or the IRB[s] if applicable) is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Tris Pharma and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

13 DATA HANDLING AND RECORD KEEPING

13.1 Inspection of Records

Tris Pharma, its designee(s), the IRB(s), or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The Investigator agrees to allow Tris Pharma, its designee(s), the IRB(s), or regulatory authorities to inspect the investigational drug storage area, investigational drug stocks, investigational drug records, subject charts and study source documents, and other records relative to study conduct.

13.2 Retention of Records

The Principal Investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

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APPENDIX A. SCHEDULE OF EVENTS

Procedure	Screening Period (up to 6 Weeks)	Baseline[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 [n]	EOT	UNS
		Day -1[o]	Day 7[o]	Day 14 [o]	Day 21 [o]	Day 28 [o]	Day 35 [o]		
Informed Consent	X								
Eligibility Assessment	X	X							
Demographics	X								
Medical History	X								
Medication History	X								
Physical Examination	X						X	X[b]	X[b]
Height and Weight[c]	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests[d]	X						X[m]	X[b]	X[b]
Drug Screening Test	X	X					X[m]		
AISRS	X	X	X	X	X	X	X[m]	X[b]	X[b]
ACDS	X	X[e]							
CGI-S	X	X	X	X	X	X	X[m]	X[b]	X[b]
DSST		X					X[m]	X[b]	X[b]
M.I.N.I. 7.0.2	X	X[e]							
Pregnancy Test[h]	X	X					X[m]	X[b]	X[b]
Vital Signs	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
12-Lead ECG[i]	X						X[m]		X[b]
C-SSRS[j]	X	X	X	X	X	X	X[m]	X	X
Questionnaire for Sleep, Appetite, Mood, and Psychotic Adverse Events		X	X	X	X	X	X[m]	X[b]	X[b]
Randomization to Study Drug IWRS		X							
Drug Dispensing		X	X	X	X	X			
DB Study Drug Titration[k]		X	X	X	X				
In-House Drug Administration						X	X		
PERMP Placement Test	X	X[e]							
PERMP Practice[k]		X	X	X	X				
Abbreviated administration of serial PERMPs						X			
Administration of serial PERMPs							X		
Drug Accountability		X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X

Procedure	Screening Period (up to 6 Weeks)	Baseline[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 [n]	EOT	UNS
		Day -1[o]	Day 7[o]	Day 14 [o]	Day 21 [o]	Day 28 [o]	Day 35 [o]		
Adverse Events	X	X	X	X	X	X	X	X	X

ACDS = Adults ADHD Clinical Diagnostic Scale; AISRS = Adult Investigator Symptom Rating Scale; CGI-I = Clinical Global Impression Scale–Improvement; CGI-S = Clinical Global Impression Scale–Severity; DB = Double-Blind; ECG = electrocardiogram; EOS = end of study; ET = Early Termination Visit; IWRS = Interactive Web Response System; M I.N.I. 7.0.2 = Mini International Neuropsychiatric Interview 7.0.2; ; PERMP = Permanent Product Measure of Performance; UNS = Unscheduled Visit.

[a] A phone call will be done to all eligible subjects within -14 to -7 days to stop stimulants within 7 days of Baseline.
[b] To be conducted if requested by the Investigator.
[c] Only weight required at Baseline and Visits 1 to 5.
[d] Laboratory tests will be done at a central lab.
[e] If not done at Screening.
[f] BP and Pulse (average of triplicate measurements), Temperature and RR.
[g] BP and Pulse (average of triplicate measurements). During Visits 4 and 5 will be taken at pre-dose and 3 hours post-dose.
[h] Serum Pregnancy Test at Screening; Urine Pregnancy Test at Baseline and at Visit 5.
[i] ECGs must be interpreted by a central reader.
[j] "Baseline" version at Screening; "Since Last visit" version for subsequent visits.
[k] PERMP practice before and after safety and efficacy assessments at Baseline and Visits 1, 2 and 3.
[m] Can be conducted at or within 2 days of Visit 5.
[n] During Visit 5, subjects who are smokers will be allowed to have up to 3 cigarette breaks.
[o] Visit Windows = ±3 days.

APPENDIX B. QUESTIONNAIRE FOR SLEEP, APPETITE, MOOD, AND PSYCHOTIC ADVERSE EVENTS

Please ask each of the 4 questions in bold font below at Baseline and Visits 1 to 5.

- If the answer is "no", circle N and go on to the next question in bold font.
- If the answer is "yes", circle Y and ask the open-ended questions in normal font, marking the descriptions as applicable either Y or N or using the free text box to record verbatim responses.

1. Have you had any changes in your sleeping since your last visit? If Yes, please tell me what you have noticed:	Y	N
a. Trouble falling asleep	Y	N
b. Trouble staying asleep	Y	N
c. Decrease in sleep quality	Y	N
d. Improvement in sleep quality	Y	N
e. Other: _____ _____		
2. Has your appetite changed since your last visit? If Yes, please tell me what you have noticed:	Y	N
a. Increased appetite	Y	N
b. Decreased appetite	Y	N
c. Other:_____ _____		
3. Has your mood been significantly different since your last visit If Yes, please tell me what you have noticed:	Y	N
a. Feeling down, depressed, or hopeless	Y	N
b. Loss of interest or pleasure in doing things	Y	N
c. More positive, cheerful, happy mood	Y	N
d. Racing thoughts or too much energy	Y	N
e. Other: _____ _____		
4. Have you had any strange or unusual thoughts or experiences since your last visit? If Yes, please tell me what you have noticed:	Y	N
a. Odd or unusual things going on that I can't explain	Y	N
b. Something interrupting or controlling my thoughts	Y	N
c. Others can read my mind	Y	N
d. Fear of people planning or about to hurt me	Y	N

e. Special natural or supernatural gifts	Y	N
f. Hearing people talking when there is no one there	Y	N
g. Hearing my own thoughts being said out loud	Y	N
h. Concerns that I might be "going crazy"	Y	N
i. Other: _____ _____		

Adaptations from: Council on Nutrition Appetite Questionnaire (CNAQ), HAM-D Rating Scale PROMIS SF v1.0 ED-Depression 8a, PROMIS SF v1.0 – Positive Affect 15a, PROMIS SF v1.0 – Sleep Disturbance 4a, Yale University PRIME Screening Test

APPENDIX C. REVISION HISTORY

Version 1.0 to Version 2.0

A major update on the study design was applied to this protocol to reflect feedback from the FDA:

"The study should be randomized and double-blind with parallel groups (i.e., not cross-over). Patients should be randomized to treatment or placebo from baseline (i.e., no open-label, "dose optimization" period should be included). Treatment arms should include fixed doses; a short, double-blind dose-titration period is acceptable. You should measure pulse, blood pressure, and weight at every clinic visit. You should use direct questioning to assess for sleep, appetite, mood, and psychotic adverse events rather than relying on spontaneous reports.

The PERMP is an acceptable outcome measure; however, you should describe the simulated work environment/testing day in the submitted protocol. Additionally, you should use the CGI-Severity at multiple time points to assess improvement rather than the CGI-I (which is prone to recall bias). From a statistical perspective, we recommend that you pre-specify the estimand and provide the rationale for your choice. You should justify that the proposed primary efficacy analysis is suitable for the chosen estimand, and pre-specify sensitivity analyses for your missing data assumptions."

DSST was included as a secondary efficacy assessment.

Version 2.0 to Version 3.0

Update to the statistical sections was applied to this protocol to reflect feedback from the FDA:

Efficacy endpoints have been updated.

ANCOVA was replaced by MMRM for primary and key secondary endpoints analyses.

Sensitivity analysis has been updated to use MI method based on missing not at random assumptions to assess impact of potential imbalances in dropouts before visit 5. Summary of PERMP-T practice scores to be provided by completers/dropouts category to check potential trends.

Sample size justification has been updated.

Primary analysis population has been updated to be a modified ITT (mITT) population which will include the subjects who have at least one PERMP-T score at Visit 5. The primary efficacy analysis and key secondary analysis will be conducted on the mITT population.

Definition of mITT population has been added.

Version 3.0 to Version 3.1	Included details on in which circumstances an additional cohort of 18 subjects will be added. Alcohol restriction has been added (from Baseline to 24 hours after Visit 5). Exclusion criteria #6 updated to : "Known history or presence of significant renal or hepatic disease, as indicated by clinical laboratory assessment (clinically significant liver function tests, blood urea nitrogen, or creatinine levels)"