CLINICAL STUDY PROTOCOL

A PHASE 3, DOSE-OPTIMIZED, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-CENTER, PARALLEL EFFICACY AND SAFETY LABORATORY CLASSROOM STUDY IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) USING CTX-1301 (DEXMETHYLPHENIDATE)

Study Number: CTx-1301-022

Drug Development Phase:	Phase 3
Investigational Product:	Dexmethylphenidate
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
IND	136674
Sponsor:	Cingulate Therapeutics [redacted]
Principal Investigator	[redacted]
Date:	Version 3.0 14 March 2023

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

Confidential Information

This document is the sole property of Cingulate Therapeutics. This document and any and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of Cingulate Therapeutics.

SUMMARY INFORMATION

Title:	A Phase 3, dose-optimized, double-blind, randomized, placebo-controlled, single center, parallel efficacy, and safety laboratory classroom study in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) using CTx-1301 (dexmethylphenidate)
Protocol Number:	CTx-1301-022
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SPONSOR PROTOCOL APPROVAL

Protocol Title:	A Phase 3, dose-optimized, double-blind, randomized, placebo-controlled, single-center, parallel efficacy, and safety laboratory classroom study in adults with Attention - Deficit/Hyperactivity Disorder (ADHD) using CTx-1301 (dexmethylphenidate)
Protocol Number:	CTx-1301-022
Protocol Version:	3.0
Date of Version:	14 March 2023

Signed for approval by:

[redacted]
Chief Medical Officer
Cingulate Therapeutics

[redacted]
Chief Science Officer
Cingulate Therapeutics

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PROTOCOL SIGNATURE PAGE

I have read and understand the contents of this clinical protocol for Study No. CTx-1301-022 dated 14 March 2023 and agree to meet all obligations of Cingulate Therapeutics as detailed in all applicable regulations and guidelines. The signature of the Investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to Good Clinical Practice [ICH 1996] and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms, and other pertinent data, will become the property of Cingulate Therapeutics.
It is agreed that the protocol contains all necessary information required to conduct the study and that the study will not be initiated without the approval of an appropriate Independent Institutional Review Board (IRB).

It is agreed that all participants in this study will provide written informed consent in accordance with the requirements specified in the Declaration of Helsinki 1964. All participants will also be informed that their medical records will be kept confidential except for review by study site personnel and appropriate IEC/IRB representatives and regulatory authorities.

In some instances, a summary of the protocol and study results, along with the names of the principal Investigator from the study site, and details of the institution with which the Investigator is affiliated will be posted in one or more publicly accessible worldwide registers at any time after the commencement of the study. The signature of the Investigator below constitutes his/her consent to have his/her name and institution disclosed should this study be made publicly available on a register. In addition, in order to avoid confusing or conflicting information, the signature of the Investigator below constitutes his/her agreement not to post information about the study on any clinical trials registry without first obtaining the prior written consent of the Sponsor/Client.

Signed By:

Principal Investigator

_____

Date of Signature

_____

Emergency Contact Information

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STUDY SYNOPSIS

Title	A Phase 3, dose-optimized, randomized, double-blind, placebo-controlled, single-center, parallel efficacy, and safety laboratory classroom study in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) using CTx-1301 (dexmethylphenidate)
Sponsor	Cingulate Therapeutics
Short Title/Acronym	Phase 3 Efficacy and Safety Adult Laboratory Classroom (ALC) Study
Protocol Number	CTx-1301-022
Investigational Product	CTx-1301, a novel, trimodal, extended-release dexmethylphenidate tablet (d-MPH)
Proposed Indication	Attention-Deficit/Hyperactivity Disorder (ADHD)
Route/Dosage Form	Oral, trimodal, extended-release tablet
Name of Active Ingredient	Dexmethylphenidate HCl (d-MPH)
Planned Study Period	Approximately 3.5 months (including screening)
Objective(s)	**Primary objective:** • To evaluate the efficacy of CTx-1301 compared to placebo in treating adults with ADHD in a laboratory classroom study **Secondary objectives:** • To determine the onset and duration of clinical effect of CTx-1301 in treating ADHD in adults in a laboratory classroom study • To determine safety and tolerability of CTx-1301 compared to placebo in a laboratory classroom study **Exploratory objectives:** • To evaluate quality and satisfaction of prior medication to investigational product
Study Design and Methodology	A single-center, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy and safety laboratory classroom study with CTx-1301 in adults with ADHD confirmed by an Adult ADHD Investigator Symptom Rating Scale (AISRS) score of at least 24 and CGI-S score of at least 4 (moderately ill) at Screening. The study will be comprised of a screening period, a dose-optimization phase, a double-blind randomized phase, and a safety follow-up phase. The Study will be comprised of 4 periods: • **Screening Period (Day -45 to Day -1):** Subjects will undergo a Screening Visit up to 45 days prior to entering the 5-week, dose-optimization phase. Only subjects who meet all inclusion and no exclusion criteria at Screening may be considered for the dose-optimization phase. A reminder telephone call will be completed 5 days prior to Day 0 of the optimization period to ensure washout of

	current prohibited medications, to confirm inclusion/exclusion criteria, and to confirm date of next visit. • **Dose-Optimization Phase (Day 0 to Day 35 ± 3 days):** During the 5-week, dose-optimization phase, subjects will have weekly visits and will be titrated to doses ranging between 25.0 – 50.0 mg of CTx-1301. Subjects starting dose will be 25.0 mg. The optimal dose will be determined with weekly visits by evaluating tolerability, safety, best individual subject dose-response using the AISRS, CGI-S, and the opinion of the Investigator. Each subject is expected to be in the dose-optimization phase for 5 weeks. Each subject is required to be on their optimal dose a minimum of 2 sequential weeks prior to the double-blind, randomized, efficacy period. Subjects will be instructed to take their dose every morning prior to 8 am over the dose-optimization period with the exception of the practice ALC visit. At the practice ALC visit, the study drug must be administered by the study staff. • **Double-blind, Placebo-Controlled, Randomized Efficacy Phase (Day 35 to Day 42 ± 3 days):** Eligible subjects will be randomized to their optimal dose (or placebo) in a 1:1 ratio after completing the practice ALC visit. Subjects will be instructed to take their assigned/randomized dose every morning over the following 7-day period with the exception of the 7th day (Visit 8). At Visit 8 (the full ALC visit), the study drug must be administered by the study staff. • **Safety Follow-Up Visit (Day 49 ± 3 days):** Subjects will have an in-clinic visit as a safety follow up; the safety follow up will be completed within 7 days (± 3 days) after the full ALC visit.
Number of Subjects/Number of Sites	Approximately 25 subjects will be enrolled in the dose optimization phase of the study; approximately 20 subjects will complete the randomized phase. The study will take place at 1 site in the United States.
Subject Selection Criteria	<u>Inclusion criteria (at Screening, unless noted otherwise):</u> 1. Male or female subjects between 18 and 55 years of age (inclusive) at the time of consent. 2. Subject must have a body mass index (BMI) ≥18.5 and ≤40. 3. Subject is unsatisfied with his/her current pharmacological therapy for treatment of ADHD or not currently receiving pharmacological therapy for ADHD. Inclusion of subjects who are naïve to pharmacological therapy for ADHD is permitted. 4. Negative serum b-human chorionic gonadotropin pregnancy test for subjects of child-bearing potential and must agree to remain abstinent or agree to use a highly effective, medically acceptable form of birth control for the time of written or verbal consent and for at least 30 days after the last dose of study drug has been taken (females) unless post-menopausal or surgically sterile. Male subjects with female partners must agree at Screening to remain abstinent or agree to use an effective and medically acceptable form of birth control from Screening to 90 days after the last dose of study drug.

	5. Subject must be in general good health defined as absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and laboratory values (hematology, chemistry, or urinalysis) at Screening. If any of the exams or values are not within the laboratory reference range, the Investigator must review range and determine if clinically relevant. If clinically relevant, the subject is not eligible for the study. 6. Subject's intellectual function is at an appropriate level, as deemed by the Investigator. 7. Subjects need to be able to perform at least the basic level of problems on the PERMP pre-test with at least 10 questions answered correctly per page or 2 minutes performed at Visit 2. 8. Subject must meet Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria for the primary diagnosis of ADHD for any of the three presentations (combined, inattentive, or hyperactive/impulsive presentation) upon clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Attention Deficit/Hyperactivity Disorder - Adults (MINI). 9. Subject must score 24 or higher on the AISRS scale at the Screening visit (Visit 1) and Baseline visit (Visit 2) if no ADHD medication washout is required. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout at the Baseline visit (Visit 2). 10. Subject must have a score of 4 (moderately ill) or higher on the clinician-administrated Clinical Global Impressions-Severity (CGI-S) scale at Screening. For subjects requiring washout of ADHD medications, this criterion refers to a score at the Baseline visit (Visit 2). 11. Subject must be able and willing to wash out of all stimulant ADHD medications (except study drug as indicated per protocol), including herbal medication, from 5 days prior to the start of the dose-optimization phase and for the duration of the entire study, defined as completion of the safety follow-up visit. Additionally, subject must be able and willing to wash out from all non-stimulant ADHD medications 21 days prior to the start of the dose optimization phase and for the duration of the entire study, defined as completion of the safety follow-up visit. 12. Subject must be able to read, write, speak, and understand English and be able to communicate with the Investigator and study coordinator in a satisfactory fashion and complete any study-related materials. Subject must plan to be available for the entire duration of the study. <u>Exclusion criteria (at Screening, except when noted otherwise) include:</u> 1. If female and of child-bearing potential, the subject must not be pregnant or breastfeeding at any time during the study or for 30 days following the completion of the study. If of child-bearing potential, urine hCG tests will be administered at protocol specified time points. Any positive pregnancy test during the study will exclude them from further participation in the study.

	2. Subject has any psychiatric diagnosis of bipolar I or II disorder, current major depressive disorder, conduct disorder, disruptive mood dysregulation disorder, intellectual disability, obsessive-compulsive disorder, eating disorder, anxiety disorder (including generalized anxiety disorder), any history of psychosis, autism spectrum disorder, Tourette's Syndrome, confirmed genetic disorder with cognitive and/or behavioral disturbances, or any other diagnosis/significant medical history that at the discretion of the Investigator excludes the subject from entry into the study. 3. Subject has evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS-related disorders that might occur in childhood, or history of persistent neurological symptoms related to a serious head injury. 4. Subject has any clinically significant and/or unstable medical abnormality, chronic medical condition, persistent neurological symptoms, history of cardiovascular abnormality, abnormalities of respiratory, hepatic, gastrointestinal, renal, or any disorder or history of a condition that would impact or interfere with drug absorption, distribution, metabolism, or excretion during the study or may interfere with the participants ability to participate in the study. 5. Subject has family history of early cardiovascular disease or sudden death. 6. Subject has any history of attempted suicide or clinically significant suicidal ideation based on the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, or answers "yes" to "Suicidal Ideation" item 4 or 5 in the past 3 years on the C-SSRS lifetime/recent assessment at Screening. 7. Subject has history of seizures, excluding febrile seizures. 8. Subject has a known primary sleep disorder (e.g., sleep apnea, narcolepsy, etc.) 9. Subject has a history of moderate to severe hypertension or has a resting sitting systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg. 10. Subject is considered treatment refractory by the Investigator or is intolerant to stimulant ADHD medication. 11. Any use of anticonvulsants currently or within the past 2 years. 12. Uncontrolled thyroid disorder indicated by thyroid stimulating hormone (TSH) ≤0.8 x the lower limit of normal (LLN) or ≥ 1.25 x the upper limit of normal (ULN) from the reference laboratory. 13. Subject has first-degree relatives (biological parent or sibling) with a history of schizophrenia, schizoaffective disorder, bipolar I disorder, or bipolar II disorder. 14. Subject has history of substance abuse or shows evidence of substance or alcohol use disorder or has a positive breath alcohol test or urine drug screen at Screening. Subjects with positive drug screens may be allowed to continue in the study if the result of the positive drug screen is from prescribed medications and the subject is willing to washout of the medication as required per protocol. 15. Subject has a history of physical, emotional, or sexual abuse resulting in a current diagnosis of posttraumatic stress disorder. 16. Previous treatment experience/exposure to CTx-1301.

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	17. Subject has a history of allergic reaction or sensitivity to methylphenidate, or any substance contained in CTx-1301 or the placebo drug. 18. Subject has participated in a laboratory study within 6 months prior to the start of Screening or has participated in any other clinical study with an investigational drug/product within 90 days prior to Screening or is currently participating in another clinical study. 19. Subject anticipates a move outside the geographic range of the investigative site during the duration of the study period or plans on travel that would not allow compliance to the protocol during the study period. 20. Subject is unsuitable in any other way to participate in the study, as determined by the Investigator. 21. Subjects who are family members of the employees at the study center, of the investigator, or those with direct involvement in the proposed study under the direction of that investigator or study center. 22. Subjects that live in the same household are not allowed to be in the same cohort. <u>Rescreening</u> Subjects may be rescreened for participation if the screen fail reason has been resolved. Subjects who are rescreened will receive a new Subject ID. Subjects are allowed to be re-screened a maximum of 1 time. Any subject who received any dose of study drug and/or are terminated early, withdraw early, or are not eligible to continue into the double-blind, randomization phase, are not allowed to be rescreened. <u>Eligibility Criteria (end of dose-optimization phase)</u> Subjects will be required to meet the following criteria at the end of the dose-optimization phase in order to be eligible for the double-blind, randomized treatment phase. These criteria are based on the efficacy and safety observed over the 5-week dose-optimization period. 1. A minimum of 2 sequential weeks on optimal dose. 2. A reduction of ≥ 30% of the AISRS from Visit 2 to Visit 7 during the dose optimization phase. 3. A CGI-I score of 1 or 2 points (“Very Much Improved” or “Much Improved”) at the end of the dose optimization phase. 4. Acceptable tolerability of the optimized CTx-1301 dose during the dose optimization phase.
Study Product and Planned Use	The active investigational product is a trimodal extended-release dexmethylphenidate (d-MPH) tablet (CTx-1301). Each tablet will contain a specified dose of d-MPH in the following strengths: • 25.0 mg • 37.5 mg • 50.0 mg All doses are the same shape and size, regardless of strength.

	CTx-1301 is a trimodal, extended-release tablet which provides an efficient use of d-MPH over the course of the day. The first release (35% of dose) consists of an immediate release (IR) with an onset of action within 30 minutes, the second release (45% of dose) is a sustained-release at approximately 3-4 hours (releasing over 60 – 90 minutes), and the third and final release (20% of dose) is an immediate release around 7-8 hours. The CTx-1301 tablet is designed to last the entire active day (up to 16 hours). During the dose-optimization phase, study drug should be administered upon wakening in the morning, no later than 8 am, due to the extended efficacy of the investigational product. Dosing is one tablet per day. All study drugs must be taken orally with approximately 240 mL of water. On the practice ALC day, all subjects will be dosed at the clinical site and are required to fast prior to dose (defined as no eating after 12 midnight the night prior to the visit). Breakfast will be provided at approximately 60 minutes (± 15 minutes) post dose and after completion of the PERMP assessment at 60 minutes. Lunch will be provided at approximately 12:00 pm ± 30 minutes. On the full ALC day (Visit 8), all subjects will be dosed at the clinical site and are required to fast prior to dose (defined as no eating after 12 midnight the night prior to the visit). Breakfast will be provided at approximately 60 minutes (+15 minutes) post dose and after completion of the PERMP assessment at 60 minutes. Lunch will be provided at approximately 12:00 ± 30 minutes. Dinner will be provided at approximately 6:00 pm ± 30 minutes.
Reference therapy	The comparator product is a matching placebo tablet. Placebo will be used if subjects are randomized to the placebo arm during the 7-day, double-blind, randomized, treatment phase.
Laboratory Classroom Days	At Visit 7, if subject meets all eligibility criteria, each subject will complete the practice ALC session with 4 PERMP assessments designed to mirror the pre-dose to 16-hour post-dose session of the full-length laboratory classroom day at Visit 8. At Visit 8, subjects will complete a full-length ALC day. The duration of the full ALC day will be approximately 17 hours, evaluating pre-dose to hour 16 using the average change in PERMP score as the primary endpoint. Pre-dose PERMP score at Visit 8 will be used as the baseline measurement for primary and secondary analysis. Visit 8 is the last day of the randomized dose (active or placebo) in the double-blind period. After completion of the treatment phase, subjects will complete a follow up safety visit.

ADHD Severity/Efficacy Evaluation Criteria	The following scales will be used during the Screening phase to assess the severity of ADHD and the math skill level of each subject: • Clinical Global Impression-Severity (CGI-S) • Mini International Neuropsychiatric Interview (MINI) • Permanent Product Measure of Performance (PERMP) Pre-Test The following scales will be used during the dose-optimization phase to globally assess the changes in ADHD severity from week to week: • Adult ADHD Investigator Symptom Rating Scale (AISRS) • Clinical Global Impressions-Severity (CGI-S) The following scales will be used to assess the efficacy of CTx-1301 versus placebo during the randomized, double-blind, treatment phase: • Permanent Product Measure of Performance (PERMP) Test • Clinical Global Impression-Severity (CGI-S)
Safety Evaluation Criteria	Adverse events, vital signs, height, and weight (z-scores), sleep evaluation, physical examinations, ECGs, clinical laboratory measurements, and C-SSRS scores will be evaluated for safety.
Duration of Subject Participation and Duration of Study Treatment	Subjects will participate in the study as outpatients for up to approximately 3.5 months (including Screening): a 45-day Screening period, a 5-week dose-optimization phase, a 7-day double-blind randomized phase, and a 7-day follow up visit. Completion of the study will be defined as completion of the last subject, last visit (LSLV) at the end of the study (Visit 9). Subjects will receive a single, daily dose of CTx-1301 during the 5-week dose-optimization phase. Subject will take the provided medication each morning during these periods, with the exception of the practice ALC day and the full ALC day, where dosing must be administered by the site staff. Subjects will be randomized at the end of the practice ALC day to either their optimal dose of CTx-1301 or placebo. Subject will take their assigned medication every morning during the 7-day randomized efficacy period (Day 35 – 42) with the exception of the morning of full ALC day as noted above.
Medication Restrictions	Subjects meeting all eligibility requirements and enrolled into the study will be subject to medication restrictions during the trial: • All ADHD stimulant medications (with the exception of study drug CTx-1301), including herbal medications, are prohibited

	from 5 days prior to the start of the dose-optimization phase to the end of the safety follow-up visit or early termination visit. These include but are not limited to all methylphenidate and amphetamine isomers and prodrugs. • All ADHD non-stimulant medications are prohibited from 21 days prior to the start of the dose-optimization phase to the end of the safety follow-up visit or early termination visit. These include, but are not limited to, atomoxetine, guanfacine, clonidine, SSRIs such as fluoxetine and paroxetine and viloxazine. • The following medications are prohibited from 21 days prior to the start of the dose-optimization phase to the end of the study or early termination visit*: o Tricyclic Antidepressants o Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., fluoxetine, paroxetine) o Benzodiazepines o Monoamine oxidase inhibitors (MAOIs) o Mood stabilizers (e.g., lithium, valproate, quetiapine) o Antipsychotics (e.g., risperidone, olanzapine) o Coumadin anticoagulants o Anticonvulsants o Halogenated anesthetics o Phenylbutazone o Any medication not described in this protocol at the discretion of the Investigator **Note: These medications may signal that an exclusionary diagnosis is present. The medical monitor should be consulted before instructing a subject to discontinue any of these medication for this study.* • Sedative hypnotics/sleep enhancers (with the exception of melatonin, if stable for 30 days prior to screening) are prohibited from 14 days prior to the start of the dose-optimization phase to the end of the study or early termination visit.* **Note: These medications may signal that an exclusionary diagnosis is present. The medical monitor should be consulted before instructing a subject to discontinue any of these medication for this study.* • Melatonin, up to 10 mg per day, is allowed if subjects have taken the medication for more than 30 days prior to Screening and are on a stable dose for the entire duration of the study. Otherwise, melatonin is prohibited from 5 days prior to the start of the dose-optimization phase to the end of the study or early termination visit.

	Medications allowed during the course of the study include the following: Nasal steroids, melatonin (if stable for 30 days prior to Screening), thyroid medication (if stable for at least 90 days prior to Screening), bronchodilators (if stable for at least 30 days prior to Screening), hormonal contraceptives for females (if stable for 30 days prior to Screening), acetaminophen, nonsteroidal anti-inflammatory medications, non-sedating antihistamines (cetirizine, loratadine, fexofenadine, etc.), mometasone, approved course(s) of prescription and nonprescription medications for the treatment of acute illnesses. Any other medication not specified in this protocol, but is considered necessary for the subject's welfare, may be allowed if it is jointly approved by the Investigator, Sponsor, and Medical Monitor. Subjects are allowed to continue cognitive and/or behavioral therapy if they have been receiving therapy for at least 30 days prior to Screening. Investigative site should attempt to obtain medical records for each subject.
Analysis Populations	Modified Intent-to-Treat (mITT) Population: All randomized subjects who receive the morning dose of double-blind study medication at Visit 8, have a pre-dose PERMP assessment at Visit 8, and have at least one post-dose PERMP assessment at Visit 8. Dose Optimization Phase Safety Population (DOS): All subjects who received at least one dose of study medication during the dose optimization phase. Double Blind Treatment Phase Safety Population (DBS): All subjects who received at least one dose of study medication during the double-blind randomized phase. Overall Safety Population (OS): All subjects who received at least one dose of study medication at any point during the study.

Criteria for Evaluation	
Efficacy Analysis	The primary and secondary efficacy evaluations are based on the PERMP scores at pre-dose and at 0.5, 1, 3, 6, 9, 12, 13, 14, 15, and 16 hours post-dose during the full ALC day at Visit 8. The baseline PERMP for primary efficacy is measured pre-dose on Visit 8. Primary Efficacy Endpoint: • Average of the change of the PERMP scores from baseline (measured pre-dose at Visit 8) to hour 16 on the full ALC day. Key Secondary Efficacy Endpoints: • Change from baseline (measured pre-dose at Visit 8) of the PERMP scores measured at each time point on the ALC day at Visit 8.

	• Change in CGI-S pre-dose at Visit 2 to post dose CGI-S at Visit 8 Exploratory efficacy endpoints will evaluate the efficacy of CTx-1301 during the dose optimization phase by assessing the following: • Evaluate overall treatment experience of subjects who were stable on ADHD stimulant medications within the 30 days prior to Screening compared to CTx-1301 at the end of dose optimization phase by utilizing the provided entrance and exit questionnaires. The purpose of this study is to estimate the effect size of treatment on the PERMP instrument in an adult ADHD population, as defined by the inclusion/exclusion criteria. Though primary and secondary endpoints are defined in accordance with ICH E9 guidelines, this study is not intended to demonstrate statistical significance via treatment group comparisons.
Safety	Safety will be analyzed for each of the safety populations. Safety endpoints include the occurrence of Treatment-Emergent Adverse Events (TEAEs) post dose. All adverse events will be listed for each subject and summarized by the body system and preferred term assigned to the event using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Any serious adverse events will be listed separately. Adverse events, vital signs, height, and weight (z-scores), physical examinations, ECG, clinical laboratory measurements, and C-SSRS scores will be evaluated for safety.
Statistical Methods	Efficacy Analysis: Primary and secondary efficacy analysis will be performed on the mITT population. Descriptive statistics for all PERMP scores and subscale scores will be calculated for each timepoint on the ALC day, and for the average of the scores collected across the ALC day. For each subject that enters the double-blind phase, the change in PERMP score from baseline (pre-dose) will be calculated at each Visit 8 post-baseline timepoint. The mean of the changes from baseline within each subject will be used in the primary efficacy analysis. The change from baseline between CTx-1301 (active) and placebo for the PERMP score will be analysed by using an ANCOVA model with treatment group as a fixed effect and baseline PERMP as a covariate. The treatment comparison will be conducted as a two-sided test at the 5% level of significance. Standard errors and 95% confidence intervals will be calculated. The other PERMP scores and subscales will be analyzed similarly to the primary endpoint.

	Safety: The frequencies of adverse events (AEs), the results of laboratory assessments, physical examinations, vital signs, height and weight, appetite, sleep, ECGs, and suicidal ideation (assessed using the C-SSRS) will be summarized by treatment in each of the safety populations. Sample size: Sample size was chosen based on recruitment feasibility, with the primary purpose of estimating the effect size of treatment on the PERMP instrument in an adult ADHD population, as defined by the inclusion/exclusion criteria. Approximately 20 subjects will be randomized into the Double-Blind phase of the study. Assuming an effect size of 1.42, 20 subjects randomized into the Double-Blind phase of the study would yield approximately 85% power to detect a difference between CTx-1301 and Placebo, assuming a significance level of 0.05. Assuming a drop-out rate of approximately 20% from the start of dose-optimization to the randomization phase, approximately 25 subjects will be required to enter the dose-optimization period of the study.

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AISRS	Adult ADHD Investigator Symptom Rating Scale
ALC	Adult Laboratory Classroom
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
CDMO	Contract Development and Manufacturing Organization
cm	Centimeters
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTx	Cingulate Therapeutics
d-MPH	Dexmethylphenidate
DA	Dopamine
DO	Dose Optimization
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FSFV	First Subject First Visit
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENT	Ears, Nose, Throat
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl transpeptidase
GI	Gastrointestinal
Hb	Hemoglobin
Hct	Hematocrit
hCG	Human chorionic gonadotropin
hr	Hour(s)
HR	Heart Rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Web Response System
ITT	Intent-To-Treat
kg	Kilograms
L	Liter
LLN	Lower limit of normal
LSLV	Last Subject Last Visit
m	Meter
ADME	Absorption, Distribution, Metabolism and Excretion

MAOIs	Monoamine Oxidase Inhibitors
MAS	Mixed Amphetamine Salts
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute
MINI	Mini International Psychiatric Interview
mL	Milliliter(s)
MMRM	Mixed-Effect Model Repeated Measure
mmHg	Millimeters of Mercury
MPH	Methylphenidate
MPV	Mean Platelet Volume
ms	Millisecond
NCS	Not Clinically Significant
NMS	Neuroleptic Malignant Syndrome
NE	Norepinephrine
PERMP	Permanent Product Measure of Performance
PP	Per Protocol
PK	Pharmacokinetic
POC	Proof of Concept
RBC	Red Blood Cell
R	Randomized Period
RS	Randomized Safety
S	Safety Period
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOC	System Organ Class
SOP	Standard Operating Procedure
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
WBC	White Blood Cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Table 1 Schedule of Assessments

Procedure / Assessments	Screening/ Washout		Dose Optimization Phase (± 3 days)					Practice ALC (± 3 days)	Double-Blind Treatment Phase Full ALC (± 3 days)	Safety Follow-up Visit (± 3 days)
Study Day	-45 to -1	-5	0	7	14	21	28	35	42	49
Visit Number	1	Phone call	2	3	4	5	6	7[j]	8	9
Informed Consent	✓									
ADHD Diagnosis and Confirmation	✓		✓[a]							
PERMP Pre-Test			✓							
Inclusion & Exclusion Criteria	✓	✓	✓							
Demographics	✓									
Medical History	✓									
Physical Examination	✓		✓							✓
Body Weight, Height, BMI[b]	✓		✓							✓
12-Lead ECG	✓[c]		✓						✓	✓[c]
Vital Signs	✓		✓	✓	✓	✓	✓	✓	✓	✓
Chemistry, Hematology, Urinalysis	✓		✓						✓	✓
Serology	✓									
Serum hCG[g]	✓									✓
Urine hCG[gh]			✓	✓	✓	✓	✓	✓	✓	
TSH	✓									
Breath Alcohol Test	✓		✓					✓	✓	

Procedure / Assessments	Screening/ Washout		Dose Optimization Phase (± 3 days)					Practice ALC (± 3 days)	Double-Blind Treatment Phase Full ALC (± 3 days)	Safety Follow-up Visit (± 3 days)
Study Day	-45 to -1	-5	0	7	14	21	28	35	42	49
Visit Number	1	Phone call	2	3	4	5	6	7[j]	8	9
Urine Screen for Drugs of Abuse	✓		✓					✓	✓	
Urine MPH Screen	✓		✓							
C-SSRS[k] Baseline/Screening	✓									
C-SSRS[k] (Since Last Visit)			✓	✓	✓	✓	✓	✓	✓	✓
MINI	✓									
AISRS	✓		✓[f]	✓	✓	✓	✓	✓[f]	✓	
PERMP assessments				✓	✓	✓	✓	✓	✓	
CGI-S	✓		✓[f]	✓	✓	✓	✓		✓	
CGI-I								✓[f]		
AE Assessment[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dose Optimization			✓	✓	✓	✓	✓			
Randomization[e]								✓[e]		
Double-Blind Study Drug Administration								✓	✓	
Drug Accountability & Compliance Assessment				✓	✓	✓	✓	✓	✓	
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Entrance/Exit Questionnaire	✓							✓		
Study Completion/Medical Sign-Off										✓

a. If subject is on medication at Screening, investigator must confirm ADHD criteria after washout of medications at baseline (Visit 2) prior to dose titration.
b. Height and weight will be measured without shoes and with light clothing using a calibrated stadiometer and scale.
c. ECG assessed at Visit 1 and Visit 9 should be off medication per washout requirements.

d. AEs will be assessed throughout the study; AEs will be collected from time the informed consent is signed until end of the study. Any AEs occurring between visits should be attributed to the next study visit (or unscheduled visit), but the dates of the AE must be recorded as occurred. AEs occurring during the washout may be reported via phone or at the following visit.
e. Randomization will occur at the end of Visit 7.
f. CGI-I, AISRS, and safety to be evaluated for eligibility prior to randomization at Visit 7.
g. Females of child-bearing potential.
h. A positive urine hCG test will be confirmed with a serum hCG. A positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study.
i. Early Termination Visit should follow the Visit 9/Day 49 visit study assessment schedule.
j. At Visit 7, the Investigator will evaluate the eligibility criteria based on the efficacy and safety observed over the 5-week dose-optimization period in the Dose Optimization Phase, for continuation into the subsequent double-blind, randomized treatment phase. If subject meets all eligibility criteria, each subject will complete the practice ALC session with 4 PERMP assessments designed to mirror the pre-dose to 16-hour post-dose session of the full-length laboratory classroom day at Visit 8.
k. Columbia Suicide Severity Rating Scale (C-SSRS): The “Baseline” version will be assessed at Screening and “Since Last Visit’ at Visits 2-9 and at Early Termination. Subjects who have, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study.

1 PRODUCT BACKGROUND INFORMATION

Methylphenidate (d,l-MPH) products have been an important treatment for ADHD for more than 70 years. The primary pharmacological effect of d,l-MPH is to increase the level of dopamine (DA) and norepinephrine (NE) in the extraneuronal space by binding to DA and NE transporters (DAT and NET, respectively) on presynaptic nerve terminals and inhibiting the reuptake of these neurotransmitters.[10,26]

All clinically used MPH formulations contained a racemic (1:1) mixture of d-threo-(R,R)-MPH and l-threo-(R,R)-MPH isomers until the enantiopure d-MPH (d-threo-(R,R)-MPH, dexmethylphenidate,) was introduced in 2002.[7] The development of enantiopure d-MPH was based on the findings that similar improvement on sustained attention was achieved after treatment with d-equivalent doses of d-MPH and d,l-MPH, but not after l-MPH.[8] Clinical efficacy was highly correlated with plasma concentrations of d-MPH. The elimination of the l-isomer does not diminish the efficacy of an acute dose of methylphenidate.[9] The efficacy of the d-isomer was equivalent to the racemic preparation in ameliorating the target symptoms of ADHD and increasing academic productivity. Thus, it was thought that the efficacy of MPH resides in the d-isomer.[8, 10, 11, 12]

The short acting form of d-MPH was released to the market[13] and demonstrated clinical efficacy lasting slightly over 5 hours in open-label studies.[14] Long-acting forms were released to the market and demonstrated clinical efficacy lasting up to 12 hours; however, a major drawback to most long-acting stimulant products currently on the market is that they do not remain therapeutically effective more than 12 hours after administration. For many patients this duration in coverage is not sufficiently long. Furthermore, as blood levels drop precipitously during the latter portions of the day, patients also may experience a crash or rebound effect, which often manifests in adverse effects such as irritability, mood changes, and worsening of clinical presentations.[25]

To alleviate the need for a mid-day dose (thereby eliminating problems related to dispensing the medication at school), a long-acting formulation of d-MPH (CTx-1301) was developed that could be administered once a day.[14]

CTx-1301 is a trimodal, extended-release tablet which provides an efficient use of d-MPH over the course of the day. The first release (35% of dose) consists of an immediate release (IR) within 30 minutes, the second release (45% of dose) is a sustained-release at approximately 3-4 hours (releasing over 60 – 90 minutes), and the third and final release (20% of dose) is an immediate release around 7-8 hours. The CTx-1301 tablet is designed to last the entire active day (up to 16 hours).

1.1 INDICATION AND CURRENT TREATMENT OPTIONS

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most prevalent psychiatric condition in children. It affects approximately 5-10% of school-aged children.[1,2,3] The hallmark set of symptoms of ADHD include inattention, hyperactivity, and impulsivity. Although ADHD was at one time considered a childhood illness that resolved in adolescence, it is estimated that up to 50% of children's symptoms persist into adolescence and beyond.[4]

Stimulants have been considered the mainstay of pharmacological treatment of ADHD for over seventy years. Their effect on disruptive behavior was discovered in 1937, when these drugs proved to increase compliance, improve academic performance, and reduce

motor activity in hyperactive children.[5] Methylphenidate (MPH) is the most frequently prescribed among stimulant agents. It has proven efficacy on ADHD symptoms.[6, 7] In addition to methylphenidate products, amphetamine products such as mixed amphetamine salts (MAS) and isolated dextroamphetamine are also commonly used to treat ADHD.[27] Finally, non-stimulant medications are also used to manage ADHD symptoms. Non-stimulant medications such as atomoxetine, clonidine, and guanfacine may be useful in patients who cannot tolerate stimulants or who may benefit from a combination of stimulant and non-stimulant combination therapy. [28]

Refer to the latest version of the CTx-1301 Investigational Brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety.

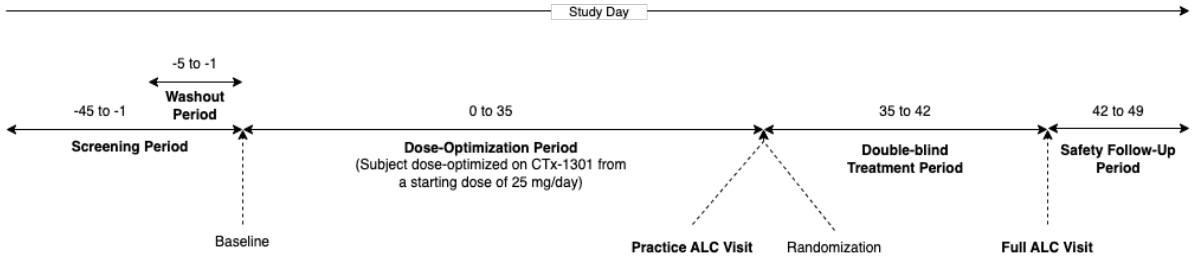
1.2 OVERVIEW OF CLINICAL STUDIES WITH CTX-1301

As part of the initial development of CTx-1301, the Sponsor conducted a proof of concept (POC) study in Scotland. The POC study was a randomized, three-arm, open-label crossover PK study in 15 healthy volunteers with a preliminary formulation. The primary objectives were to confirm the time and site of radiolabel release of the second and third doses of CTx-1301 and to provide PK data on blood plasma levels of d-MPH. Secondary objectives of this study were to compare the PK profiles of the LD, FocalinXR®, to CTx-1301, and to determine the gastrointestinal transit parameters of CTx 1301. Each subject received one dose of 10 mg FocalinXR® (Treatment A) and two doses of 12.5 mg CTx-1301, one with a radiolabeled second dosage layer (Treatment B) and one with a radiolabeled core dosage layer (Treatment C). In general, this study successfully demonstrated the trimodal release of d-MPH from CTx-1301, and absorption, distribution, metabolism, and excretion (ADME) parameters were consistent with those seen in the published literature.

The sponsor also conducted CTx-1301-001, the pivotal comparative BA study, which demonstrated bridging to the LD (FocalinXR®) and allows reliance on the previous findings of the LD for safety. The comparative BA study evaluated the lowest dose of FocalinXR® (5 mg) to the lowest dose of CTx-1301 (6.25 mg) and the highest dose of FocalinXR® (40 mg) to the highest dose of CTx-1301 (50.0 mg). This study was completed with 39 ADHD patients and each patient received all 4 doses. The primary objectives of this study were to compare the bioavailability of the listed drug, FocalinXR® to CTx-1301 in a fasted state as well as to evaluate dose proportionality of CTx-1301. Secondary objectives were to characterize the PK of d-MPH blood plasma levels after dosing as well as to evaluate safety. This study successfully demonstrated bridging, dose-proportionality, and safety of CTx-1301.

2 STUDY PURPOSE AND OBJECTIVES

2.1 STUDY DESIGN SCHEMATIC



2.2 STUDY PURPOSE

The purpose of this study is to evaluate the efficacy and safety of CTx-1301 for treatment of ADHD in adults aged 18-55 years in a laboratory classroom setting. Results from prior studies of CTx-1301 demonstrate that it is well tolerated. This study will provide additional data regarding the safety and efficacy of CTx-1301 at multiple dosage strengths as well as over time.

2.3 PRIMARY OBJECTIVE

- To evaluate the efficacy of CTx-1301 compared to placebo in treating adults 18-55 years old with ADHD in a laboratory classroom study

2.4 SECONDARY OBJECTIVE(S)

- To determine the onset and duration of clinical effect of CTx-1301 in treating ADHD in adults 18-55 years old in a laboratory classroom study
- To determine safety and tolerability of CTx-1301 compared to placebo in a laboratory classroom study

2.5 EXPLORATORY OBJECTIVES

- Evaluate overall treatment experience of subjects who were stable on ADHD stimulant medications within the 30 days prior to Screening compared to CTx-1301

3 INVESTIGATIONAL PLAN AND DESIGN

3.1 STUDY DESIGN

The study design is a single-center, dose-optimized, double-blind, randomized, placebo-controlled, laboratory classroom efficacy and safety study with CTx-1301 in adults (18 – 55) with ADHD confirmed by an AISRS score of at least 24 at Screening. The study will be comprised of a 45-day Screening period, a 5-week dose-optimization phase, a 7-day double-blind, randomized, efficacy phase, and a safety follow-up visit.

The Study will be comprised of 4 periods:

- Screening Period (Day -45 to Day -1): Subjects will undergo a Screening Visit up to 45 days prior to entering the 5-week, dose-optimization period. Only subjects that meet all inclusion and no exclusion criteria at Screening may be considered for the dose-optimization period.
- Dose-Optimization Period (Day 0 to Day 35 ± 3 days): Subjects that meet all inclusion and no exclusion criteria at Day 0 may be considered for the dose-optimization period. During the 5-week dose-optimization period, subjects will have weekly visits and will be titrated to doses ranging between 25.0 – 50.0 mg of CTx-1301. Subjects' starting dose will be 25.0 mg. The optimal dose will be determined with weekly visits by evaluating tolerability, safety, best individual subject dose-response using the AISRS, CGI-S, and the opinion of the Investigator. Each subject is expected to be in the dose-optimization phase for 5 weeks, thus allowing one extra week if subjects require adjustment to achieve their "optimized dose", including a lower dose or a higher dose during the optimization phase. Each subject is required to be on their optimal dose a minimum of 2 sequential weeks prior to the 7-day, double-blind, randomized, efficacy period. Visit 7 is the last day of the dose optimization period. At Visit 7, the investigational medication must be administered by the site. On the practice ALC day (Visit 7), subjects are required to fast prior to dose (defined as no eating after 12 midnight the evening prior to Visit 7). Breakfast will be provided at approximately 60 minutes post dose (+15 minutes), following the 60-minute post-dose PERMP assessment. Lunch will be provided at approximately 12:00 pm (± 30 minutes).
- Double-blind, Randomized, Efficacy Phase (Day 35 to Day 42 ± 3 days): Prior to randomization of the double-blind treatment at Visit 7, confirm subjects are eligible to continue onto the double-blind, randomized phase. Eligible subjects will be randomized to either their optimal CTx-1301 dose, or placebo. The randomized dose of CTx-1301 will be the final optimized dose as determined during the dose-optimization phase (active), or placebo. All subjects will receive their assigned treatment for 7 days (± 3 days). All efficacy assessments will be performed after the last dose of the randomized, efficacy phase at Visit 8. At Visit 8, the investigational medication must be administered by the site. On the full ALC day (Visit 8), subjects are required to fast prior to dose (defined as no eating after 12 midnight the evening prior to Visit 8). Breakfast will be provided at approximately 60 minutes post dose (+15 minutes), following the 60-minute post-dose PERMP assessment. Lunch will be provided at approximately 12:00 pm (± 30 minutes) and dinner will be provided at approximately 6:00 pm (± 30 minutes).
- Safety Follow-Up Visit (Days 42 to Day 49 ± 3 days): a follow-up visit (Visit 9) will be conducted after Visit 8 to ensure safety of all subjects.

3.2 RATIONALE FOR STUDY DESIGN

This study will investigate the safety and efficacy of CTx-1301 in 18 to 55 year-old subjects in a laboratory classroom study design. Laboratory classroom studies include a controlled environment with structured activities provided throughout the day, designed to provoke behaviors associated with ADHD symptoms and yield quantifiable outcomes. This design allows for documented assessments of drug effects over multiple timepoints during the assessment day.

4 STUDY POPULATION

4.1 SOURCE AND NUMBER OF SUBJECTS

The study site will recruit potential subjects from its database and via local advertising and medical referrals if required.

Assuming a dropout rate of 20%, approximately 25 subjects will be required to enter the dose-optimization period of the study to achieve completion of approximately 20 subjects.

Subjects may be rescreened once for participation if the screen fail reason is resolved. Subjects who are rescreened will receive a new Screening number. Subjects are allowed to be re-screened a maximum of 1 time. Any subject who received any dose of study drug, are terminated early, withdraw early, or are not eligible to continue into the double-blind, randomization phase, are not allowed to be rescreened.

Dropouts will not be replaced.

4.2 CRITERIA FOR EVALUATION

Eligibility of subjects for study enrollment will be based on the results of a Screening medical history, physical examination, mental state examinations, vital signs (blood pressure and pulse), the inclusion/exclusion criteria as described below, breath alcohol test, urine drugs of abuse, and clinical laboratory tests. All Screening tests will be performed and assessed by qualified study staff. The nature of any conditions present at the time of the physical and mental state examinations and any pre-existing conditions will be documented as medical history.

4.3 INCLUSION CRITERIA

1. Male or female subjects between 18 and 55 years of age (inclusive) at the time of consent.
2. Subject must have a body mass index (BMI) ≥18.5 and ≤40.
3. Subject is unsatisfied with his/her current pharmacological therapy for treatment of ADHD or not currently receiving pharmacological therapy for ADHD. Inclusion of subjects who are naïve to pharmacological therapy for ADHD is permitted.
4. Negative serum b-human chorionic gonadotropin pregnancy test for subjects of child-bearing potential and must agree to remain abstinent or agree to use a highly effective, medically acceptable form of birth control for the time of written or verbal consent and for at least 30 days after the last dose of study drug has been taken (females) unless post-menopausal or surgically sterile. Male subjects with female partners must agree at Screening to remain abstinent or agree to use an effective and medically acceptable form of birth control from Screening to 90 days after the last dose of study drug.
5. Subject must be in general good health defined as absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and laboratory values (hematology, chemistry, serology, TSH, or urinalysis) at Screening. If any of the exams or values are not within the laboratory reference range, the Investigator must review range and determine if clinically relevant. If clinically relevant, the subject is not eligible for the study.
6. Subject's intellectual function is at an age-appropriate level, as deemed by the Investigator.

7. Subjects need to be able to perform at least the basic level of problems on the PERMP pre-test with at least 10 questions answered correctly per page or 2 minutes performed at Visit 2.
8. Subject must meet Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria for the primary diagnosis of ADHD for any of the three presentations (combined, inattentive, or hyperactive/impulsive presentation) upon clinical evaluation and confirmed by the MINI International Neuropsychiatric Interview for Attention Deficit/Hyperactivity Disorder - Adults (MINI). The MINI should also be used to evaluate any other psychiatric disorders.
9. Subject must score 24 or higher on the AISRS scale at the Screening visit (Visit 1) and Baseline visit (Visit 2) if no ADHD medication washout is required. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout at the Baseline visit (Visit 2).
10. Subject must have a score of 4 (moderately ill) or higher on the clinician-administrated Clinical Global Impressions-Severity (CGI-S) scale at Screening. For subjects requiring washout of ADHD medications, this criterion refers to a score at the Baseline visit (Visit 2).
11. Subject must be able and willing to wash out of all stimulant ADHD medications (except study drug as indicated per protocol), including herbal medication, from 5 days prior to the start of the dose-optimization phase and for the duration of the entire study, defined as completion of the safety follow-up visit. Additionally, subject must be able and willing to wash out from all non-stimulant ADHD medications 21 days prior to the start of the dose optimization phase and for the duration of the entire study, defined as completion of the safety follow-up visit.
12. Subject must be able to read, write, speak, and understand English and be able to communicate with the Investigator and study coordinator in a satisfactory fashion and complete any study-related materials. Subject must plan to be available for the entire duration of the study.

Eligibility Criteria (end of dose-optimization phase)

Subjects will be required to meet the following additional eligibility criteria at the end of the dose-optimization phase (Visit 7) in order to enter the double-blind, randomized phase. These criteria are based on the efficacy and safety observed over the 5-week dose-optimization period.

1. A minimum of 2 sequential weeks on optimal dose.
2. A reduction of ≥30% reduction of the AISRS from Visit 2 to Visit 7 during the dose-optimization phase.
3. A Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2 points (“Very much improved” or “Much improved”) at the end of the dose optimization phase.
4. Acceptable tolerability of the optimized CTx-1301 dose during the optimization phase.

4.4 EXCLUSION CRITERIA

1. If female and of child-bearing potential, the subject must not be pregnant or breastfeeding at any time during the study or for 30 days following the completion of the study. If of child-bearing potential, urine hCG tests will be administered at protocol specified time points. Any positive pregnancy test during the study will exclude them from further participation in the study.
2. Subject has any current psychiatric diagnosis of bipolar I or II disorder, major depressive disorder, conduct disorder, disruptive mood dysregulation disorder, intellectual disability, obsessive-compulsive disorder, eating disorder, anxiety disorder (including generalized anxiety disorder), any history of psychosis, autism spectrum

disorder, Tourette's Syndrome, confirmed genetic disorder with cognitive and/or behavioral disturbances, or any other diagnosis/significant medical history that at the discretion of the Investigator excludes the subject from entry into the study.

3. Subject has evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS-related disorders that might occur in childhood, or history of persistent neurological symptoms related to a serious head injury.
4. Subject has any clinically significant and/or unstable medical abnormality, chronic medical condition, persistent neurological symptoms, history of cardiovascular abnormality, abnormalities of respiratory, hepatic, gastrointestinal, renal, or any disorder or history of a condition that would impact or interfere with drug absorption, distribution, metabolism, or excretion during the study or may interfere with the participants ability to participate in the study.
5. Subject has family history of early cardiovascular disease or sudden death.
6. Subject has any history of attempted suicide or clinically significant suicidal ideation based on the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, or answers "yes" to "Suicidal Ideation" item 4 or 5 during the past three years on the C-SSRS lifetime/recent assessments at Screening.
7. Subject has history of seizures, excluding febrile seizures.
8. Subject has a known primary sleep disorder (e.g., sleep apnea, narcolepsy, etc.)
9. Subject has a history of moderate to severe hypertension or has a resting sitting systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg.
10. Subject is considered treatment refractory by the Investigator
11. Any use of anticonvulsants currently or within the past 2 years.
12. Uncontrolled thyroid disorder indicated by thyroid stimulating hormone (TSH) ≤0.8 x the lower limit of normal (LLN) or ≥ 1.25 x the upper limit of normal (ULN) from the reference laboratory.
13. Subject has first-degree relatives (biological parent or sibling) with a history of schizophrenia, schizoaffective disorder, bipolar I disorder, or bipolar II disorder.
14. Subject has history of substance abuse or shows evidence of substance or alcohol use disorder or has a positive breath alcohol test or urine drug screen at Screening or Baseline. Subjects with positive drug screens may be allowed to continue in the study if the result of the positive drug screen is from prescribed medications and the subject is willing to washout of the medication as required per protocol.
15. Subject has a history of physical, emotional, or sexual abuse resulting in a current diagnosis of posttraumatic stress disorder.
16. Previous treatment experience/exposure to CTx-1301.
17. Subject has a history of allergic reaction or sensitivity to methylphenidate, or any substance contained in CTx-1301 or the placebo drug.
18. Subject has participated in a laboratory classroom study within 6 months prior to the start of Screening or has participated in any other clinical study with an investigational drug/product within 90 days prior to Screening or is currently participating in another clinical study.
19. Subject anticipates a move outside the geographic range of the investigative site during the duration of the study period or plans on travel that would not allow compliance to the protocol during the study period.
20. Subject is unsuitable in any other way to participate in the study, as determined by the Investigator.
21. Subjects who are family members of the employees at the study center, of the investigator, or those with direct involvement in the proposed study under the direction of that investigator or study center.
22. Subjects that live in the same household are not allowed to be in the same cohort.

4.5 SUBJECT WITHDRAWAL CRITERIA

Subjects have the right to withdraw from the study at any time for any reason. The Investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, adverse events (AEs) or treatment failure after a prescribed procedure, protocol deviations, administrative or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study data uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Should a subject decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible. Regardless of the reason for withdrawal, a complete final evaluation should be made at the time of withdrawal, including an explanation of why the subject is withdrawing from the study.

The primary reason for removal or withdrawal of a subject from the study must be recorded on the electronic case report form (eCRF). If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test should also be recorded on the electronic case report form (eCRF). Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

4.6 SUBJECT REPLACEMENT

Subjects may be rescreened once for participation if the screen fail reason is resolved. Subjects who are rescreened will receive a new Subject ID; however, their original Subject ID and screen fail reason must be documented. Subjects are allowed to be re-screened a maximum of 1 time. Any subject who received any dose of study drug and are terminated early, withdraw early, or are not eligible to continue into the double-blind, randomization phase, are not allowed to be rescreened. Drop-outs will not be replaced.

4.7 TREATMENT AND SUBJECT RESTRICTIONS

4.7.1 Study Medication

Subject will self-administer the study drug daily on an outpatient basis for the full duration of the study, beginning on the first day of the dose-optimization phase (Visit 2) and ending at Visit 7. At Visit 7 (practice ALC visit) and Visit 8 (full ALC visit), the study staff will administer the dose.

Study drug should be administered upon wakening in the morning, no later than 8 am, due to the extended efficacy of the investigational product. Dosing is one tablet per day. Study drug should not be altered in any way (crushed, chewed, divided, etc.).

On the practice ALC day (Visit 7), subjects are required to fast prior to dose (defined as no eating after 12 midnight prior to Visit 7). At Visit 7, breakfast will be provided at approximately 60 minutes post dose (+15 minutes), just following the PERMP assessment at 60 minutes post dose. Lunch will be provided at approximately 12:00 pm (± 30 minutes). On the full ALC day (Visit 8), subjects are required to fast prior to dose (defined as no eating after 12 midnight prior to Visit 8). At Visit 8, breakfast will be provided at 60 minutes post dose (+15 minutes), just following the PERMP assessment at 60 minutes post dose. Lunch will be provided at approximately 12:00 pm (± 30 minutes) and dinner will be provided at approximately 6:00 pm (± 30 minutes).

If a subject forgets to take a dose prior to 8 am, the subject should skip the dose and resume taking the medication the following day. Due to the extended efficacy of CTx-1301, study drug should not be taken later than 8 am. Subject should not make up a missed dose by taking more than one tablet/day; medication is restricted to a single dose/tablet each day.

All subjects will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment, safety of the patient, and successful outcomes of the study. The proper use of study medication and adherence will be reviewed at all visits via a Drug Accountability and Compliance Assessment.

4.7.2 Medications and treatments

Subjects meeting all eligibility requirements and who are enrolled in the study will be subject to medication restrictions during the trial:

- All ADHD stimulant medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the dose-optimization phase to the end of the study (Visit 9) or early termination visit. These include but are not limited to all methylphenidate and amphetamine isomers and prodrugs.

- All ADHD non-stimulant medications are prohibited from 21 days prior to the start of the dose-optimization phase to the end of the study (Visit 9) or early termination visit. These include, but are not limited to, atomoxetine, guanfacine, viloxazine and clonidine.

- The following medications are prohibited from 21 days prior to the start of the dose-optimization phase to the end of the study (Visit 9) or early termination visit*:

    - Tricyclic Antidepressants
    - Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., fluoxetine, paroxetine)
    - Monoamine oxidase inhibitors (MAOIs)
    - Benzodiazepines
    - Mood stabilizers (e.g., lithium, valproate, quetiapine)
    - Antipsychotics (e.g., risperidone, olanzapine)
    - Coumadin anticoagulants
    - Anticonvulsants
    - Halogenated anesthetics
    - Phenylbutazone
    - Any medication which would make subject excluded from study (see exclusion criteria)

    **Note: These medications may signal that an exclusionary diagnosis is present. The medical monitor should be consulted before instructing a subject to discontinue any of these medications for this study.*

- Sedative hypnotics/sleep enhancers (with the exception of melatonin, if stable for 30 days prior to screening) are prohibited from 14 days prior to the start of the dose-optimization phase to the end of the study (Visit 9) or early termination visit.

    **Note: These medications may signal that an exclusionary diagnosis is present. The medical monitor should be consulted before instructing a subject to discontinue any of these medication for this study.*

- Melatonin, up to 10 mg per day, is allowed if subjects have taken the medication for more than 30 days prior to screening and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to the start of the dose-optimization phase to the end of the study (Visit 9) or early termination visit.

ALLOWED TREATMENTS:

Medications allowed during the course of the study include the following: nasal steroids, melatonin (if stable for 30 days prior to Screening), thyroid medication (if stable for at least 90 days prior to Screening), bronchodilators (if stable for at least 30 days prior to Screening), hormonal contraceptives for females (if stable for 30 days prior to Screening), acetaminophen, nonsteroidal anti-inflammatory medications, non-sedating antihistamines (cetirizine, loratadine, fexofenadine, etc.), mometasone, approved course(s) of prescription and nonprescription medications for the treatment of acute illnesses. Any other medication not specified in this protocol, but is considered necessary for the subject's welfare, may be allowed if it is jointly approved by the Investigator, Sponsor, and Medical Monitor.

Subjects are allowed to continue cognitive and/or behavioral therapy if they have been receiving therapy for at least 30 days prior to Screening.

Subjects will be questioned on compliance with restrictions during Screening, prior to and during the dose-optimization phase, prior to and during the double-blind, randomization phase, and the safety follow up. The Investigator will determine whether a deviation from the restrictions warrants the subject's withdrawal from the study. All deviations should be documented in the CTMS.

All medications will be coded using World Health Organization Drug Dictionary (WHO-DD). Information on the format and version of the coding dictionary will be provided in the data management plan and the statistical analysis plan.

5 STUDY TREATMENTS: ASSIGNMENT & SUPPLY MANAGEMENT

5.1 STUDY TREATMENTS

5.1.1 Identity of study treatments

The active investigational product is a trimodal, modified-release dexmethylphenidate (d-MPH) tablet (CTx-1301). Each tablet will contain a specified dose of d-MPH in the following strengths:

- 25.0 mg
- 37.5 mg
- 50.0 mg

CTx-1301 is a trimodal, modified-release tablet, which provides d-MPH in 3 releases over the course of the day. The first release (35% of dose) consists of an immediate release (IR) with an onset of action within 30 minutes, the second release (45% of dose) is a sustained-release at approximately 3-4 hours (releasing over 60 – 90 minutes), and the third and final release (20% of dose) is an immediate release around 7-8 hours. The CTx-1301 tablet is designed to last the entire active day (up to 16 hours).

5.1.2 Selection of doses

All subjects will be titrated to their optimal dose during the dose-optimization phase. Subjects starting dose will be 25.0 mg. The optimal dose will be determined with weekly visits by evaluating tolerability, safety, best individual subject dose-response using the AISRS (since the prior visit), CGI-S, and the opinion of the Investigator. Each subject is expected to be in the dose-optimization phase for 5 weeks and be on their optimal dose for 2 sequential weeks prior to the randomized efficacy period.

Possible doses are: 25.0, 37.5, or 50.0 mg of CTx-1301. In the 7-day, randomized efficacy portion of the study, subject will receive their optimal dose (as determined in the dose-optimization phase), or placebo.

5.1.3 Administration

- Study drug (1 tablet) should be taken orally, upon wakening, at approximately the same time each day, and prior to 8 am.
- All study drugs will be given orally with approximately 240 mL (1 cup) of water.
- The tablet is to be swallowed whole; no alteration of the tablet is allowed (crushing, chewing, dividing, etc.).

5.1.4 Dose schedule

In the dose-optimization phase once daily treatments of CTx-1301 will be administered orally in the morning for titration to an optimal daily CTx-1301 dose. It is recommended that dosing takes place upon wakening, at approximately the same time each day and no later than 8 am in the morning due to the extended efficacy of the investigational product.

Subjects will be randomized (1:1) to their optimal dose or placebo in the 7-day, double-blind, randomized, efficacy phase at the end of the practice ALC visit (Visit 7) after confirming eligibility requirements.

The daily dose of CTx-1301 in the randomized phase will be the same as the optimal dose of CTx-1301 as determined at the end of the dose-optimization phase (Visit 7); 25.0, 37.5, or 50.0 mg of CTx-1301, or placebo.

5.1.5 Dose modification

No alteration of the tablet is allowed (crushing, chewing, dividing, etc.) at any time during the study. Modifications to the strength of CTx-1301 subjects received are allowed only at protocol-specified times (i.e., dose-optimization phase) and only at the discretion of the Investigator. No modification to the strength of CTx-1301 is allowed during the double-blind randomized phase of the study.

5.1.6 Treatment compliance

Subjects must agree to take the study medication daily as detailed per the protocol. Compliance with the study drug will be monitored and determined at each visit. Subjects

will be instructed to bring all unused study drug with them to all visits. Compliance will be assessed by counting tablets and dividing the actual number of doses taken (per tablet count) by the number of doses the subject should have taken within a visit period and multiplying by 100. Subjects who miss more than 25% of scheduled doses or take more than 125% of scheduled doses will be considered non-compliant and will be reviewed and evaluated by the Investigator. Evidence of non-compliance must be immediately reported to the Sponsor or Sponsor's designee. Noncompliance issues will be discussed with the subject and at the Investigator's discretion, may result in termination from the study. All subjects will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment, safety, and successful outcomes of the study.

5.1.7 Overdosage

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. For the purposes of this clinical trial, overdosage is defined as the administration of a supratherapeutic dose, a daily dose of the study drug which is larger than the highest dose used in the study, i.e., 50.0 mg. Notifications of subjects taking more than one tablet of study drug per day (irrespective of dose size) will be provided by the study site to the Sponsor or Sponsor's representative before the end of the next business day after learning of the discrepancy. The Sponsor will review with the Medical Monitor and investigator to determine if subject can continue in the study. Overdose *per se* is not an AE; however, any clinical sequelae of an overdose should be reported as an AE (and an SAE, if appropriate). See Section 8.1.2 for reporting instructions.

Known signs and symptoms after acute overdosage of d-MPH, resulting primarily from overstimulation of the central nervous system and from excessive sympathomimetic effects include: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by a coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrythmias, hypertension, mydriasis, and dryness of mucous membranes (FocalinXR® Package Insert 2019).

5.1.8 Rescue therapy

No rescue therapy is applicable for this study.

5.1.9 Risks

The perceived risks involved in this study relate to:

Drug

Inclusion/exclusion criteria and the dose-optimization phase have been included in order to minimize possible risks in relation to administration of CTx-1301 (d-MPH).

The most common adverse reactions after taking d-MPH (FocalinXR®) capsules (at least 5% and twice the incidence among placebo-treated patients) are dry mouth, dyspepsia, headache, and anxiety for adult patients. Any adverse reactions to CTx-1301 are expected to be similar to those of FocalinXR®.

Table 2 shows the treatment-emergent adverse events resulting from a placebo-controlled, double-blind-group study in pediatrics with ADHD at a flexible FocalinXR® dose of 5-30 mg per day. Only events that occurred in 5% or more of the patients treated with FocalinXR®.and were at least twice the incidence in placebo-treated patients.

Table 2 Treatment-Emergent Adverse Events Occurring during Double-Blind Treatment (Adults)

	Focalin XR 20 mg N=57	Focalin XR 30 mg N=54	Focalin XR 40 mg N=54	Placebo N=53
No. of Subjects with AEs				
Total	84%	94%	85%	68%
Primary system Organ Class / Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

The following adverse reactions may also occur:

Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia

Gastrointestinal: abdominal pain, nausea

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: leukopenia and/or anemia

Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood, aggressive behavior, libido changes

Skin/Subcutaneous: scalp hair loss

Urogenital: priapism
Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS.

Further information can be found in the FocalinXR®. Extended-Release Package Insert.

Blood Sampling

Blood samples for safety will be taken at Screening for eligibility, Baseline and again at the last in-clinic study visit (Visit 9). There is a risk of bruising and fainting during blood sampling.

5.2 STUDY TREATMENT ASSIGNMENT

During the 5-week dose-optimization phase, subjects will have weekly visits and will be titrated to doses ranging between 25.0 – 50.0 mg of CTx-1301. Subjects starting dose will be 25.0 mg, based on PI discretion, previous medical history, and prior stimulant medications. The optimal dose will be determined with weekly visits by evaluating tolerability, safety, best individual subject dose-response using the AISRS, CGI-S, and the opinion of the Investigator. An IRT system will be used to track each subject's optimization of drug during the dose optimization phase.

The treatment given to individual subjects during the double-blind, randomized, efficacy phase of the study, is determined by a randomization schedule; the randomization schedule will assign eligible subjects to 1 of 2 treatment groups and be in an allocation ratio of 1:1 (active: placebo). The actual treatment assigned to each subject is executed by an IRT system utilizing the randomization schedule. All investigational products (active and placebo) will appear identical to ensure blinding.

5.2.1 Enrollment Procedure

Subjects who meet all inclusion and none of the exclusion criteria at Screening will be enrolled into the dose-optimization phase. Subjects who meet inclusion criteria at the end of the dose-optimization phase will continue into the double-blind, randomization phase. Subjects will be randomized via IRT to their optimal dose or placebo at the end of Visit 7.

5.2.2 Blinding procedure and code breaks

During the blinded study period, all study drugs, regardless of strength (CTx-1301 and placebo) are identical in color, shape, size, and packaging in order to maintain the blind.

All subjects, Sponsor personnel, Investigator staff, and Sponsor representatives involved in the daily operations of the study will remain blinded to the identity of the treatment from time of randomization until database lock and subsequent unblinding by using the following methods:

1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the unblinded biostatistician and Clinical Trials Material Management Personnel

2) The identity of the treatments will be concealed by the use of study drugs (active/placebo) that are all identical in packaging, labeling, schedule of administration, and appearance.

In the event that breaking the blind may be essential to permit appropriate treatment of a subject's medical condition:

- The Investigator should contact the Medical Monitor by phone to discuss
- The Medical Monitor will provide their recommendation to unblind or not to unblind
- Ultimately, the Investigator will make the final determination whether to unblind the treatment allocation for the welfare of the subject
- If unblinding is deemed necessary, the Investigator should consult with the appropriate unblinded study personnel
- Every effort should be made to ensure that unblinding information is not shared with blinded study team members

5.3 STUDY TREATMENT SUPPLIES MANAGEMENT

5.3.1 Interactive Response Technology (IRT) for Investigational Product Management

An IRT will be utilized during this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, site-assignments, subject randomizations, returns, and emergency unblinding of the investigational product.

An IRT user manual and training will be provided to each site, detailing instructions for use on IRT.

5.3.2 Shipping, Manufacture, Packaging, and Labeling

Manufacturing of study treatments will be carried out by the CDMO vendor according to internal SOPs and approved manufacturing procedures. The CDMO vendor will ship study drug to the packaging facility for subsequent packaging, labeling, and shipping to the sites.

The packaged tablets will be shipped and stored in a secured, temperature-monitored environment between 20 – 25 °C (68 – 77°F). Excursions are permitted from 15-30°C (59-86°F) as long as they do not exceed 24 hours; excursions exceeding 24 hours must be reported immediately to the Sponsor or Sponsor's representative. Deviations from the storage requirements must be documented and reported to the Sponsor or Sponsor's representative. Investigational product must be quarantined and not used until Sponsor reviews the deviation and provides documentation if it is permissible to use the study drug.

The study drug will be shipped in 10-ct bottles. The labels will include, but will not be limited to, the following information: study number, quantity, dosing instructions, and precautionary labeling as required by FDA on all investigational drugs per CFR 21 Subpart A, Section 312.6.

5.3.3 Accountability of study supplies

Sufficient amounts of the Investigational Product (IP) for the study will be provided to the site. The investigator or qualified designee will acknowledge receipt of the IP investigational product and document the content of the shipment including quantity, temperature, and condition. The Investigator or designee will maintain a full record of study treatment accountability. An Investigational Product Dispensing and Accountability Log should be kept up to date with the following information:

- The identification of the subject number to whom the study treatment was dispensed.
- The date and time the study treatment was dispensed to the subject.
- Any deviations from the IP dispensing (if applicable).

Study supplies should be reconciled with this record and the shipping quantities. All IP must be accounted for at all times via documentation that accurately records all IP that is received, dispensed, administered, returned to site, and returned to Sponsor (or Sponsor's representative). Any unused materials must be returned as per Sponsor requirements.

It is ultimately the Investigator's responsibility to dispense and administer (when applicable) IP. These tasks may be assigned to a qualified designee who has been sufficiently trained and works closely under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form. The Investigator or designee will dispense the IP only to the subject. Subjects will receive enough IP to last them until the next in-clinic visit. Subjects must return any/all unused study drug to the site at their next scheduled visit. Dispensing and return of study drug will be recorded on the CRFs and Dispensing and Accountability Log.

The Investigator or designee will be required to have a valid DEA Form 223 certificate of registration for Scheduled II Controlled Substances for the duration of the study and be able to order and distribute Scheduled II Controlled Substances via a valid DEA Form 222.

No IP supplied by the Sponsor (stock product or returned from subject) may be removed from the site where originally shipped without the knowledge and approval of the Sponsor. If transfer of IP is approved by the Sponsor, the site must document the transfer and follow all local, state, and national laws regarding shipment of Scheduled II Controlled Substances.

At the end of the study, or as instructed by the Sponsor, all unused stock and subject-returned IP are to be sent to a Sponsor representative or nominated contractor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the Sponsor (or Sponsor's representative) prior to shipping to the designated contractor. If there is unused supply in which the original packaging is verified as intact, the bottle should not be opened and the amount on the label will be used instead of a physical count. Prior to shipment, the Sponsor and/or Sponsor's representative should be contacted for authorization to return any IP. Shipment of all IP must follow local, state, and national laws regarding shipment of Scheduled II Controlled Substances. The drug accountability forms maintained by the site will allow for reconciliation of IP, both used and returned. The Sponsor should be notified immediately if there is any discrepancy involving IP accountability.

5.3.4 Storage of study treatment supplies

All study drugs must be stored in compliance with the label requirements and in a secure place with limited and controlled access.

Throughout the duration of the study, the temperature of the storage locations will be monitored and recorded daily. The packaged tablets will be stored in a secured, temperature-monitored environment between 20 – 25 °C (68 – 77°F). Excursions are permitted from 15-30°C (59-86°F) as long as they do not exceed 24 hours; excursions exceeding 24 hours must be reported immediately in the IRT system. Investigational

product must be quarantined and not used until Sponsor reviews the deviation and provides documentation if it is permissible to use the study drug.

6 METHODS, MEASUREMENTS, EVALUATIONS, AND STUDY-RELATED PROCEDURES

6.1 INFORMED CONSENT

The Investigator, or designated study staff, must obtain written (signed and dated) informed consent from each subject prior to their participation in this study. Informed consent will be obtained after full explanation of the aims, methods, objectives, and potential hazards of the study.

The Investigator, or designated study staff, must also explain to the subject that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent must be obtained prior to any study procedures being conducted. The Investigator, or designated study staff, should sign and date the consent form to confirm that the consent process was completed correctly, and the subject has fully understood the objectives of the study as well as the risks.

The subject will be provided with a copy of their signed and dated consent form, along with any other written information, which they should be instructed to retain. The original will be stored with the subject's source documents.

If, during a subject's participation in the trial, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Subjects should be provided with a copy of the signed and dated amended consent form.

A washout period may be required to discontinue any prohibited medication. A subject cannot be instructed to washout of any medication for this study until after the signed informed consent is obtained.

Screening procedures may take place across multiple days to allow enough time to complete all procedures and confirm subject eligibility. Screening procedures and dates should be documented in the source documents as well as in the eCRF's.

6.2 ADHD DIAGNOSIS AND CONFIRMATION

The investigator will confirm the subject meets the criteria for the primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) per the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) upon clinical evaluation and confirmed by the MINI International Neuropsychiatric Interview for Attention Deficit/Hyperactivity Disorder - Adults (MINI). In addition, the subject must score 24 or higher on the AISRS scale and a 4 or higher on the clinician-administrated Clinical Global Impressions-Severity (CGI-S) scale at the Screening if the subject is not receiving treatment for ADHD. For all subjects the AISRS score must be $\geq$24 and the CGI-S score must be $\geq$4 at the Baseline visit (Visit 2). Screening can occur across multiple days. Adequate washout of stimulant ADHD medications will be defined as no medication for the previous 5 days. Adequate washout of non-stimulant ADHD medications will be defined as no medication for the 21 days prior to Day 0.

6.3 DEMOGRAPHICS

The Investigator, or designee, will record each subject's date of birth, sex, and race.

6.4 MEDICAL HISTORY

The Investigator, or designated study staff, will take a detailed medical history from each subject at Screening. Details of any relevant medical or surgical history, including allergies or drug sensitivity, will be recorded. Any concomitant medications will also be recorded. Other medications taken 30 days prior to the Screening visit should be recorded with start and stop dates. All lifetime psychoactive medications and lifetime nonpharmacological interventions (e.g., cognitive, or behavioural therapy) should be recorded. A diagnosis of ADHD is an inclusion criterion and should be recorded as part of the Subject's Medical History in the eCRFs.

6.5 PRIOR AND CONCOMITANT TREATMENTS

All non-study treatment including but not limited to herbal treatments, vitamins, prescription medication, nonpharmacological treatment (e.g., cognitive, or behavioral therapy), received within 30 days prior to Screening will be recorded as a prior medication on the appropriate eCRF page. Any treatments received between Screening and the EOS (Visit 9) will be recorded as a concomitant medication on the appropriate eCRF page. If a treatment is received both within the 30 days prior to Screening and also between Screening and EOS, it should be recorded as both a prior and concomitant treatment.

The subject's lifetime ADHD medication history and the subject's lifetime nonpharmacological interventions (e.g., cognitive and/or behavioral therapy) for ADHD will be documented.

6.6 PRIOR ADHD MEDICATION QUESTIONNAIRE

The site, in consultation with the subject, will be asked about prior medical history and response utilizing stimulant medications.

6.7 POST-TREATMENT QUESTIONNAIRE

The site, in consultation with the subject, will be asked about their response to the study drug dosed in this study.

6.8 PHYSICAL AND NEUROLOGICAL EXAMINATIONS

The Investigator, or medically qualified designee, will perform the physical examination at protocol-specified times, which will include assessment of the following body systems:

- General appearance
- Skin
- Head, Eyes, Ears, Nose and Throat
- Neck and Spine
- Psychiatric
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal

- Central Nervous System (CNS)/Neurological
- Lymph nodes
- Thyroid

The outcome of these assessments will be documented in the source and eCRF and any abnormalities will be described. Changes in physical exam from the Screening visit will be recorded as an AE, if deemed clinically significant by the Investigator. See Section 8.1.2 for AE reporting.

6.9 HEIGHT, WEIGHT, AND BODY MASS INDEX (BMI)

Body weight and height will be recorded at protocol-specified times within the eCRF. Weight will be measured in kilograms (kg) while wearing street clothes and without shoes. All weight measurements should be taken with the same calibrated scale and recorded to the nearest tenth of a kilogram. Subject must have a body mass index (BMI) ≥18.5 and ≤40.

Height will be measured in centimeters (cm) without shoes. All height measurements should be taken with the same calibrated stadiometer and recorded to the nearest centimeter. (See Table 1 for schedule of assessments).

Any clinically significant changes in height, weight, or BMI from Screening will be recorded as an AE, if deemed clinically significant by the Investigator. See Section 8.1.2 for AE reporting.

6.10 VITAL SIGNS

Arterial blood pressure, heart rate, and temperature will be recorded at Screening and at all in-clinic study visits. Prior to obtaining blood pressure and heart rate measurements, the subject should be at rest for a minimum of 5 minutes. Vital signs will be checked at each in-clinic visit for clinical safety and recorded in the eCRF.

The Investigator can interpret individual findings based on the subject's age, physical state, and level of fitness. Subjects with readings marginally outside the normal range[30] may be included in the study if, in the Investigator's opinion, these are not clinically significant (NCS); this decision will be documented in the eCRF. Any clinically significant value observed after Screening must be reported as an AE. See Section 8.1.2 for AE reporting.

6.11 CLINICAL LABORATORY TESTS

The Investigator, or appropriately trained study staff, will collect blood samples for hematology and biochemistry analysis as well as a urine sample for urinalysis at Screening, Baseline, Visit 8, and Visit 9 (or early termination); blood sample for serology and TSH will only be collected at screening. Values for the laboratory safety tests must be within normal ranges, as defined by an accredited laboratory facility, or considered not clinically significant by a medically qualified designee at Screening to be eligible. The results of these tests must be available before subjects are enrolled into the dose-optimization phase. If additional clinical laboratory tests are performed in addition to the protocol-required tests, they must be recorded in the source documents and eCRF.

The following tests will be carried out:

Hematology
White Blood Cell (WBC) and differential, Red Blood Cell (RBC), Hemoglobin (Hb), Hematocrit (Hct), Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH), Mean Platelet Volume (MPV), Mean corpuscular hemoglobin concentration (MCHC), platelets

Biochemistry
Sodium, potassium, chloride, BUN, creatinine, BUN/Creatinine ratio, alkaline phosphatase, bilirubin, albumin, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose.
Thyroid
Thyroid Stimulating Hormone (TSH)

Serology
Hep-B and Hep-C

Urinalysis
Color, Clarity, Bilirubin, ketones, glucose, proteins, blood, nitrite, pH, specific gravity, and leukocytes.

Urine Screen for Drugs of Abuse and Breath Alcohol Test
At Screening (Visit 1), Day 0 (Visit 2), Day 35 (Visit 7), and Day 42 (Visit 8) urine samples will be tested for drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, THC, cocaine, and opioids) and a breath alcohol test will be conducted; urine samples will be tested for methylphenidate at Screening (Visit 1) and Day 0 (Visit 2). If the tests are positive for alcohol and/or drugs of abuse at Screening or Day 0 (Visit 2), the subject must be excluded from study participation, with the exception of the subject's current ADHD medication (at Screening only). Subjects are required to washout of their ADHD medications prior to Baseline (Visit 2).

Pregnancy Test
Pregnancy tests will be performed for all female subjects of childbearing potential. A serum hCG pregnancy test will be performed at Visit 1 and Visit 9 (or early termination visit). A urine hCG will be performed at Visits 2-8. A positive pregnancy test will exclude a subject from participation in the study. A positive urine hCG test will be confirmed with a serum hCG pregnancy test.

If a lab test result is outside of normal range, the test may be repeated at the Investigator's discretion. If a lab test result at EOS has changed significantly from Screening and is deemed clinically significant (CS) by the Investigator, it should be recorded as an AE. See Section 8.1.2 for AE reporting.

Subjects will be advised to follow up with their primary physician regarding any CS laboratory finding or other event of medical significance (as judged by the Investigator).

6.12 ECG

ECGs will be administered at Visit 1, Visit 2, Visit 8, and Visit 9 (or early termination visit). Visit 1 and Visit 9 ECGs should be obtained when subject is not on ADHD medication, per protocol. All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be recorded prior to drawing blood samples (if applicable to visit). All attempts should be made to use the same ECG recorder for all visits for individual subjects. The

initial read of the ECG will be done immediately by the Investigator after collection to ensure the safety of subjects. A repeat ECG is optional and may be administered at the discretion of the Investigator.

Standard 12-lead ECG will record heart rate (HR), PR interval, RR interval, QT interval, QTc with Bazett correction (QTcB) and QTc with Fredericia correction (QTcF) intervals, and QRS duration.

6.13 COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a tool designed to systemically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over identification of suicidal behavior. The C-SSRS will be administered by a trained rater at the site.

This study will utilize 2 versions of the C-SSRS. At the Screening visit, the lifetime/recent version "Baseline/Screening" will be completed; for all subsequent visits, the “Since Last Visit” version of the C-SSRS will be administered. The outcome of these assessments will be documented in the eCRF.

Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the Investigator for follow up. Any potential subject deemed to be at risk will be excluded from the study.

Any clinically significant value observed after dosing must be reported as an AE. See Section 8.1.2 for AE reporting.

6.14 STUDY EVALUATIONS AND ASSESSMENTS

All rating scales and assessments, including the AISRS, C-SSRS, PERMP, CGI-S, MINI, and CGI-I should be completed by the same Investigator (or appropriate designee) whenever possible. All clinicians who administer these scales and/or assessments will be trained, experienced with the scale/assessment, and approved by the Sponsor prior to administration.

Study site personnel in the ALC study involved in the PERMP are only to interact with subjects in the ALC sessions. These study personnel may not participate in the collection of any other invasive or noninvasive procedures inside or outside of the classroom for the entire duration of the study.

6.14.1 AISRS

The Adult ADHD Investigator Symptom Rating Scale (AISRS) is a widely used, 18-item, validated, semi-structured, clinician-rated scale that evaluates the severity of both hyperactivity and inattentive ADHD in symptoms. The AISRS will be administered at Visits 1 – 8 to assess the changes in ADHD severity from week to week.

6.14.2 CGI-S

The CGI-S is a clinician-rated scale that evaluates the severity of psychopathology (ADHD symptoms in the study) on a scale from 1 (not at all ill) to 7 (among the most severely ill) (Busner and Targum 2007). The CGI-S will be completed at Visits 1 – 6 and Visit 8 (depending on adequate washout of medication).

6.14.3 PERMP

The Permanent Product Measure of Performance (PERMP) is an objective, validated, skill-adjusted math test that measures attention in ADHD. The PERMP total score comprises the sum number of math problems attempted, and the number of math problems answered correctly. A higher PERMP score indicates lower impairment. PERMP pre-test will be administered on Day 0 to determine the appropriate math level to be assigned during the practice ALC visit. PERMP practice tests will be administered at Visits 3-6. The practice ALC visit will determine the final level of math for each subject that will be used for the full ALC day on Visit 8.

6.14.4 MINI

The MINI International Neuropsychiatric Interview for Attention Deficit/Hyperactivity Disorder - Adults is a structured diagnostic interview for making diagnoses included in the Diagnostic and Statistical Manual of Mental Disorders and is an accurate structured psychiatric interview. The MINI will be administered by a trained clinician at the site.

The MINI will be administered at Screening to confirm the diagnosis of ADHD in conjunction with the AISRS and CGI-S. In addition, the interview can be used to identify any other presenting diagnosis which may be clinically significant and/or exclusionary. The outcome of these assessments will be documented in the eCRF. Any potential subject deemed to be at risk for other exclusionary psychiatric diagnosis will be excluded from the study.

6.14.5 CGI-I

The CGI-I is a clinician-rated scale that evaluates the total improvement of the patient condition relative to baseline due to drug treatment on a scale from 1 (Very Much Improved) to 7 (Very Much Worse). The CGI-I will be completed at the end of the dose-optimization period to assess eligibility for randomization into the double-blind treatment period.

6.15 DESCRIPTION OF OTHER STUDY PROCEDURES

6.15.1 Drug Accountability and Compliance

Compliance with the study drug will be monitored and determined at each in-office visit. Subjects will be instructed to bring all unused study drug and used/empty packaging with them to all visits. Compliance will be assessed by counting tablets and dividing the actual number of doses taken (per tablet count) by the number of doses the subject should have taken within a visit period and multiplying by 100. Details of compliance assessments will be appropriately documented by designated site personnel. Subjects who miss more than 25% of scheduled doses or taken more than 125% of scheduled doses will be considered non-compliant and will be reviewed and evaluated by the Investigator. Evidence of non-compliance must be immediately reported to the Medical Monitor. Noncompliance issues will be discussed with the subjects, and at the Investigator’s discretion, may result in termination from the study. All subjects will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment, safety of the patient, and successful outcomes of the study.

6.15.2 Blood Sampling

Blood samples for safety will be taken at Screening and Baseline for eligibility and again at the last in-clinic visit (Visit 9). The total blood volume taken at each time point will be approximately 4 mL. An additional 1 mL may be needed if using a cannula (waste volume). There is a risk of bruising and fainting during the blood sampling procedure.

6.15.3 Study Completion/Medical Sign-Off

Completion of the study will be defined as completion of the last subject, last visit (LSLV) at the end of the safety follow-up visit (Visit 9). Following completion of the safety follow-up visit (Visit 9), the Investigator will perform a medical sign-off for each subject.

6.16 DURATION OF THE STUDY

Subjects will participate in the study as outpatients for approximately 3.5 months: a 45-day Screening period, a 5-week dose-optimization phase, a 7-day double-blind treatment phase, and a follow-up safety assessment visit.

Completion of the study will be defined as completion of the last subject, last visit (LSLV) at the end of the safety follow-up visit (Visit 9).

Subjects will receive a single, daily dose of CTx-1301 during the 5-week dose-optimization phase. During the 7-day, double-blind, randomized, efficacy phase of the study, subjects will be randomized to their optimal dose of CTx-1301 or placebo.

7 STUDY SCHEDULE

7.1 SCREENING (DAY -45 TO -1)

Subjects will be evaluated at their Screening Visit to determine whether or not they are eligible to enroll into the dose-optimization phase of the study. Subjects who are adequately washed out of ADHD medications (stimulants and non-stimulants) will be administered the AISRS and CGI-S. Subject who are not washed out of ADHD medications at Screening (stimulants and non-stimulants) must wash out and come back in for another day to obtain the AISRS and CGI-S for eligibly (after an adequate wash out of ADHD medications is confirmed). These subjects will be deemed eligible or not eligible prior to Visit 2.

Subjects may be re-screened a maximum of 1 time when the subject may still be a suitable candidate for the study and the reason for screen failure may be resolved (e.g., out-of-range clinical laboratory results, insufficient medication washout, etc.).

7.1.1 Visit 1 (Screening Visit)

Subjects will be evaluated at their Screening Visit to determine their eligibility to enroll into the study. The following study-related procedures will be performed:

- Obtain Informed Consent
- Confirmation of ADHD Diagnosis utilizing AISRS (score of ≥ 24), and CGI-S (score of ≥4)
- Administer the C-SSRS (Baseline/Screening Version)
- Administer the MINI

- Administer the Prior Medication Questionnaire
- Review Inclusion and Exclusion Criteria
- Collect Demographics
- Collect Medical History, including Prior and Concomitant Medications
- Perform Physical Examination
- Collect Body Weight, Height, and BMI
- Collect Vital Signs
- Perform 12-Lead ECG
- Collect blood and urine samples for Chemistry, Hematology, TSH, Serology, and Urinalysis
- Perform a Urine Screen for Methylphenidate
- Perform a Urine Screen for Drugs of Abuse
- Perform a Breath Alcohol Test
- Perform a Serum Screen for hCG in females of child-bearing potential
- Assess for Adverse Events
- Remind Subjects that they must Washout of ADHD Medications 5 days prior to the start of the dose-optimization phase (Visit 2)

All rating scales and assessments for each individual subject should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible.

7.1.2 Washout Call

The washout call should be initiated after clinical lab test results and 12-lead ECG results from Screening have been received, reviewed, and subject is confirmed eligible. Eligible subjects will be contacted by a member of the site staff and provided with instructions on discontinuing any protocol-prohibited medications. During the washout, a subject's current prohibited medications (if applicable) will be discontinued for a period of a minimum of 5 times the half-life of the medication.

The site personnel should perform the following procedures on the washout call:

- Schedule and/or confirm Visit 2 (Day 0)
- Review Inclusion/Exclusion criteria
- Review concomitant medications. If new concomitant medications that require washout are reported, instructions for appropriate washout will be provided.
- Provide/remind instructions on discontinuing any medication requiring washout
- Determine if any AEs have occurred since Screening

7.2 DOSE-OPTIMIZATION PHASE (VISITS 2-7)

During the dose-optimization phase, Subjects will have weekly visits (Visit 2 – Visit 7) and will be titrated to doses ranging between 25.0 – 50.0 mg of CTx-1301. The subjects' starting dose will be 25.0 mg. The optimal dose will be determined weekly by evaluating tolerability, safety, best individual subject dose-response using the AISRS, CGI-S, and the opinion of the Investigator.

Subject will self-administer the study drug on an outpatient basis for the full duration of the study, beginning on the first day of the dose-optimization phase and ending at Visit 7. Study drug will be administered by the site on Visits 7 and 8.

Study drug (1 tablet) should be taken orally, upon wakening, no later than 8 am, and at approximately the same time each day with approximately 240 mL of water. Study drug should not be altered in any way (crushed, chewed, divided, etc.).

Each subject is expected to be in the dose-optimization phase for 5 weeks thus allowing one extra week if subjects require adjustment to their "optimized dose", including a lower dose or a higher dose during the optimization phase. Each subject is required to be on their optimal dose a minimum of 2 sequential weeks prior to the 7-day, randomized, double-blind, efficacy period.

7.2.1 Visit 2

Visit 2 is the first visit of the dose-optimization phase.

The following study-related procedures will be performed:

- Confirmation of ADHD Diagnosis utilizing AISRS (score of ≥ 24) and CGI-S (score of ≥4)
- Review Inclusion and Exclusion Criteria
- Perform Physical Examination
- Collect Body Weight, Height, and BMI
- Collect Vital Signs
- Perform 12-Lead ECG
- Collect Blood and Urine samples for Chemistry, Hematology, and Urinalysis
- Perform a Urine Screen for Drugs of Abuse
- Perform a Breath Alcohol Test
- Perform a Urine Screen for Methylphenidate
- Perform a Urine hCG in females of child-bearing potential
- Administer the C-SSRS (Since Last Visit Version)
- Administer PERMP pre-test
- Dispense Dose (CTx-1301)
- Record Concomitant Medications
- Assess for Adverse Events

All rating scales and assessments for each individual subject should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible.

7.2.2 Visit 3 – Visit 6

Drug Accountability and Compliance Assessments will begin at Visit 3 and continue at each Visit throughout the entire course of the study. Visits during the remainder of the dose-optimization phase (Visit 3 through Visit 6) will include the following study-related procedures:

- Collect Vital Signs
- Perform a urine hCG in females of child-bearing potential
- Administer the C-SSRS (Since Last Visit Version)
- Administer the AISRS
- Administer the CGI-S
- Evaluate optimal dose
- Dispense Dose (CTx-1301)

- Drug Accountability and Compliance Assessment
- Record Concomitant Medications
- Assess for Adverse Events
- Administer 2 PERMP Practice Tests

All rating scales and assessments for each individual subject should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible.

7.2.3 Visit 7

At Visit 7, the Investigator will evaluate the eligibility criteria based on the efficacy and safety observed over the 5-week dose-optimization period in the Dose Optimization Phase, for continuation into the subsequent double-blind, randomized treatment phase. If subject meets all eligibility criteria, each subject will complete the practice ALC session with 4 PERMP assessments designed to mirror the pre-dose to 16-hour post-dose session of the full-length laboratory classroom day at Visit 8.

Study drug will be administered by study staff at Visit 7. Subjects should fast from 12 midnight the prior evening. The subject will be provided breakfast by the site approximately 60 minutes (+15 minutes) post-dose and after completion of the PERMP at 30 minutes. Lunch will be provided by the site at approximately 12:00 pm (± 30 minutes).

The following study-related procedures will be performed:

- Collect Vital Signs
- Perform a Urine Screen for Drugs of Abuse
- Perform a Breath Alcohol Test
- Perform a urine hCG in females of child-bearing potential
- Administer the C-SSRS (Since Last Visit) version
- Administer the AISRS
- Administer CGI-I
- Administer the Medication Exit Questionnaire
- Drug Accountability and Compliance Assessment
- Study staff to administer Dose (optimized CTx-1301) @ 7:00 AM (± 5 minutes)
- Record Concomitant Medications
- Assess for Adverse Events
- 4 ALC sessions, including PERMP assessments, conducted at approximately 30 minutes pre-dose and at 0.5, 1, 3, and 6 hours post-dose [all ± 5 minutes]
- Randomization to CTx-1301 or Placebo via IRT
- Dispense Double-Blind Study Drug Dose (CTx-1301 or Placebo)

All rating scales and assessments for each individual subject should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible.

7.3 RANDOMIZED LABORATORY CLASSROOM STUDY

7.3.1 Visit 8

Study drug will be administered by study staff at Visit 8. Subjects should fast from 12 midnight the prior evening. Breakfast will be provided by the site approximately 60 minutes post-dose (+15 minutes), and after completion of the PERMP at 30 minutes post dose (7:30am). Lunch will be provided by the site at approximately 12:00 pm (±30 minutes). Dinner will be provided by the site at approximately 6:00 pm (±30 minutes).

- Collect Vital Signs
- Perform 12- Lead ECG
- Collect blood for Chemistry, Hematology, and Urinalysis
- Perform a Urine Screen for Drugs of Abuse
- Perform a urine hCG in females of child-bearing potential
- Perform a Breath Alcohol Test
- Administer the C-SSRS (Since Last Visit Version)
- Administer the AISRS
- Administer CGI-S
- Drug Accountability and Compliance Assessment
- Record Concomitant Medications
- Assess for Adverse Events
- Study staff to administer Double-Blind Study Drug Dose (CTx-1301 or Placebo) @ approximately 7:00 AM (± 5 minutes)
- 11 ALC sessions, including PERMP assessments, conducted at approximately 30 minutes pre-dose and at 0.5, 1, 3, 6, 9, 12, 13, and 14, 15, and 16 hours post-dose [all ± 5 minutes]

All rating scales and assessments for each individual subject should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible.

7.4 SAFETY FOLLOW-UP VISIT

7.4.1 Visit 9

During the safety follow-up visit, subjects will be evaluated for overall safety.

The following study-related procedures will be performed:

- Collect Body Weight, Height, and BMI
- Perform a Physical Exam
- Perform 12-Lead ECG
- Collect Vital Signs
- Collect blood and urine samples for Chemistry, Hematology, and Urinalysis
- Perform a Serum Screen for hCG in females of child-bearing potential
- Administer the C-SSRS (Since Last Visit Version)
- Record Concomitant Medications
- Assess for Adverse Events
- Study Completion/Medical Sign-Off

All rating scales and assessments for each individual subject should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible.

7.5 EARLY TERMINATION

Early Termination Visits should follow the Visit 9 procedures, if possible.

7.6 UNSCHEDULED VISITS

Investigator may require a subject to undergo an unscheduled visit if required for safety and/or efficacy during the study. Subjects may contact the clinic and request an unscheduled visit to address safety and/or efficacy between scheduled visits, if necessary. All procedures conducted at an unscheduled visit must be recorded in Electronic Data Capture (EDC).

7.7 SUBJECTS LOST TO FOLLOW-UP

When a subject is lost to follow-up at any time during the study prior to the last scheduled visit (Visit 9), three attempts must be made to contact the subject. These attempts must be documented and at least one attempt must include communication in writing which asks the subject to return to the site to undergo EOS procedures and return any remaining investigational drug. The written communication will be sent to the subject's address via mail or courier with an acknowledgment of receipt request.

8 SAFETY MEASUREMENTS AND EVALUATIONS

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator and site staff are responsible for detecting, documenting, and reporting events that meet the definition of an Adverse Event, Serious Adverse Event, or Suspected Unexpected Serious Adverse Reaction.

8.1.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational product whether or not considered related to the investigational product. Symptoms of the disease under study should not be considered AEs if they are part of the expected vacillation/progression of the disease. However, significant worsening of the symptoms should be recorded as an AE. The Investigator should use professional judgement in deciding whether a symptom is a normal, expected event associated with the disease or is an AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding if collected after dosing), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational product.

All AEs are collected from the time of the informed consent is signed until the end of the study. All AEs must be followed to conclusion of the AE or no further improvement is expected.

Events meeting the definition of an AE include, but are not limited to:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New condition(s) detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study. A thorough medical history should be taken to limit observation of conditions that were present prior to dosing.

- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose *per se* should not be reported as an AE/SAE).

Events that do not meet the definition of an AE **include**:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience/prescheduled admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Clinical AEs will be described by diagnosis and not by symptoms, when possible (e.g., upper respiratory tract infection (URTI), seasonal allergy, etc. instead of runny nose).

Serious adverse event

An SAE is any untoward medical occurrence that, at any dose:

a) Results in death.

b) Is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the Investigator's office or out-patient setting. Complications that occur during hospitalization are considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is

serious. When in doubt as to whether “hospitalization” occurred and/or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse or reports of spontaneous abortion.

8.1.2 Reporting adverse events and serious adverse events

Time period for reporting adverse events and serious adverse events

AEs will be collected from the time the subject signs the Informed Consent Form until the end of the study.

SAEs will be collected over the same time period as stated above for AEs and will be reported to the Sponsor within 24 hours of the Investigator or designee becoming aware of the situation.

Medical conditions existing prior to consent should be recorded as part of the subject’s medical history.

Reporting adverse events

AEs will be recorded in detail on the AE source document and collected in the electronic data capture (EDC) system.

Medical conditions reported by the subject that meet the definition of an AE must also be recorded if not previously well-characterized by the Investigator/physician in the subject’s medical history.

Adverse events will be collected as reported by the subjects for the duration of the study.

8.1.3 Adverse event grading and assessments

Intensity grading

All AEs will be graded on a three-point scale and reported in detail as indicated on the CRF:

- Mild – easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities
- Moderate – sufficiently discomforting to interfere with normal everyday activities
- Severe – incapacitating and/or prevents normal everyday activities

Expectedness

All AEs must be assessed as to whether they are expected to occur or unexpected. The Medical Monitor must evaluate expectedness based on current knowledge as found in the protocol, the investigator brochure, product insert, or label of other methylphenidate drugs.

- Unexpected –severity and nature of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- Expected – event is known to be associated with the intervention or condition under study.

Relationship assessment

Study treatment relationship for each AE should be determined by the Investigator using the following explanations:

- Not related – The event is clearly not related to the investigational agent/procedure – i.e., another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.
- Possibly related – The event follows a reasonable temporal sequence from the time of investigational product administration; and/or follows a known response pattern to the study treatment; but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Definitively related – The event follows a reasonable temporal sequence from the time of investigational product administration; and follows a known response pattern to the investigational product; and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; and either occurs immediately following investigational product administration, or improves on stopping the investigational product, or reappears on repeat exposure, or there is a positive reaction at the application site.
- Non-dosing procedure - The event is not related to the study drug but is related to the subject's participation in the study in another capacity, for example: bruising due to venipuncture.

Outcome Assessment

The outcome for each AE should be determined by the Investigator using the following explanations:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

Duration

The date (and time, if available) of the start and end of adverse events will be recorded.

Follow-up

Any AEs ongoing at the end of the study, which are considered in any way related to the study medication or the study regime, will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

In addition, any SAEs will be followed up to resolution (or other criteria outlined above). If any serious related event is not resolved (or does not meet any other criteria outlined above) prior to the completion of the final study report, the report will be issued. If additional information becomes available following the completion of the report, an addendum will be generated detailing the follow-up information. Any follow-up information on SAEs must be reported to the Sponsor within 24 hours of the investigator or study site staff becoming aware of additional information.

Reporting serious adverse events

Within 24 hours after SAE detection, observation, or report of occurrence (regardless of the relationship to test article), the Investigator or designee will enter the SAE into EDC. The Investigator or designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to the appropriate Sponsor contact. If the EDC system is temporarily unavailable, the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

If EDC is not functional, a paper SAE form will be utilized and provided to the following contact:

Email: [redacted]
SAE Fax Line: [redacted]
SAE Help Line: [redacted]

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demographics
- Description of events, with diagnosis if available

- Investigator opinion of relationship to study treatment
- Criterion for seriousness

The following are desirable and are of particular relevance for assessment of the adverse event report:

- Date of onset of SAE
- Date SAE stopped, if relevant
- Study treatment start date
- Study treatment end date, if relevant
- Action taken on study treatment
- Outcome, if known

The initial report will be followed up with more information as relevant. This may require the Investigator to obtain copies of hospital case reports, autopsy reports, and other documents as applicable. If required, any hospital records/reports, admission reports, etc., pertaining to the SAE must be redacted prior to sending to the sponsor.

Reporting of SUSARs

Where the adverse reaction is unexpected and serious it may be termed Suspected Unexpected Serious Adverse Reaction (SUSAR). Study site personnel should ensure all relevant information is provided to the Sponsor to allow the Sponsor to meet their obligations to report any SUSAR to the relevant competent authority.

SUSARs will be reported, by the site, to the Principal Investigator and Sponsor within 24 hours of the site first becoming aware of the event. The Sponsor or designee will then carry out reporting as follows:

SUSARs which are fatal or life-threatening: reporting to the Ethics Committee and FDA within 7 days of becoming aware of the event. A more detailed report will be provided within an additional 8 days.

All other SUSARs: reporting to the Ethics Committee and FDA within 15 days of first becoming aware of the event.

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 will be reported to the FDA by Sponsor with an IND Safety report within 7 days. The IRB will be notified of the alert reports per FDA regulations.

8.2 PREGNANCY

Females with a positive pregnancy test will be excluded from further participation in the study. Pregnancies will be recorded in the appropriate module of the eCRF. In the event the eCRF is not available, a paper copy of pregnancy report must be provided to the following contact:

[redacted]
Email: [redacted]
SAE Fax Line: [redacted]
SAE Help Line: [redacted]

All pregnancies will be followed to at least the completion/termination of the pregnancy. The investigator will document the subject visits accordingly and record the information in the clinical site's source documents. If the pregnancy continues to delivery, the outcome (health of the infant), in addition to the maternal health status, must be included in the report.

Pregnancy will not be considered an AE or SAE. Any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

8.3 LABORATORY EVALUATIONS RELATED TO SAFETY

Clinical safety laboratory assessments (hematology, biochemistry, and urinalysis) will be conducted at Visit 1, Visit 2, and Visit 9 (or early termination, if applicable) to ensure the subject's good health; laboratory assessments for serology and TSH will be conducted at Visit 1. Abnormal results that the Investigator considers to be clinically significant, other than those observed at Screening (medical history), will be recorded as an AE.

Clinically significant findings in laboratory tests at Screening (Visit 1) and Baseline (Visit 2) will be considered pre-existing conditions (medical history), as well as failure to meet eligibility criteria. Subjects will be instructed to follow up with their primary physician for any medical event or condition discovered at Screening, which, in the opinion of the screening physician, is clinically significant.

8.4 VITAL SIGNS, PHYSICAL EXAM, ECGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs, Physical Exams, and ECGs will be assessed at Screening and protocol-specified times throughout the study to ensure the subject is, and remains in, good general health. Abnormal findings that the Investigator (or central reader for ECGs) considers to be clinically significant, other than at Screening, will be recorded as an AE.

9 DATA MANAGEMENT AND STATISTICAL ANALYSIS METHODS

9.1 DATA COLLECTION

The investigators authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit the site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by appropriate and qualified site personnel. Data collection procedures will be discussed at the site initiation visit and/or the investigator's meeting. Once a subject is screened, it is expected that the site personnel will complete the data entry as soon as possible after the subject visit to ensure accuracy and completeness of the data.

9.2 CLINICAL DATA MANAGEMENT

Data are to be entered per the CRO's Data Management Plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using both computerized and manual procedures.

9.3 STATISTICAL ANALYSIS PROCESS

The study will be analyzed by the sponsor and/or agent of the sponsor.

The Statistical Analysis Plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics, and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also address how missing, unused, and spurious data will be addressed. The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analysis will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.4 SAMPLE SIZE CALCULATION

The primary hypothesis is that the test drug (CTx-1301) is superior when compared to placebo. The null and alternative hypothesis are as follows:

H_o: The change from Visit 8 baseline in PERMP scores at Visit 8 Hour 16 post-dose does not differ between CTx-1301 and placebo.

H_a: The change from Visit 8 baseline in average PERMP scores across Visit 8 Hour 16 post-dose differs between CTx-1301 and placebo.

Sample size was chosen based on recruitment feasibility, with the primary purpose of estimating the effect size of treatment on the PERMP instrument in an adult ADHD population, as defined by the inclusion/exclusion criteria. Approximately 20 subjects will be randomized into the Double-Blind phase of the study. Assuming an effect size of 1.42, 20 subjects randomized into the Double-Blind phase of the study would yield approximately 85% power to detect a difference between CTx-1301 and Placebo, assuming a significance level of 0.05.

Assuming a drop-out rate of approximately 20% from the start of dose-optimization to the randomization phase, approximately 25 subjects will be required to enter the dose-optimization period of the study.

9.5 ANALYSIS POPULATIONS

The analysis populations are defined below. In the randomized portion of the study, subjects will be analyzed based on the treatment to which they are randomly assigned.

Modified Intent-to-Treat (mITT) Population: All randomized subjects who receive the morning dose of double-blind study medication at Visit 8, have a pre-dose PERMP assessment at Visit 8, and have at least one post-dose PERMP assessment at Visit 8.

Dose Optimization Phase Safety Population: All subjects who received at least one dose of study medication during the dose titration phase.

Double Blind Treatment Phase Safety Population: All subjects who received at least one dose of study medication during the double-blind randomized phase.

Overall Safety Population: All subjects who received at least one dose of study medication at any point during the study.

9.6 DATA ANALYSIS

9.6.1 Subject Disposition

Subject disposition will be summarized for all randomized subjects. Subjects who complete the study and discontinue from the study will be summarized. The reason for discontinuation from the study will also be presented.

9.6.2 Drug Exposure and Compliance

A descriptive summary will be performed for exposure to study medication. Treatment compliance will be determined and summarized descriptively within each study phase and overall using the appropriate safety population.

9.6.3 Demographic and Baseline Characteristics

Baseline data, relevant screening data, and demographic characteristics will be summarized for the safety and mITT populations.

9.6.4 Medical History

Medical history will be coded using the Medical Dictionary Activities (MedDRA). Subject history will be coded by system organ class (SOC) and preferred term (PT) and will be summarized using the safety population. A diagnosis of ADHD is an inclusion criterion and should be recorded as part of the Subject's Medical History in the CRFs.

9.6.5 Psychiatric History

Psychiatric history will be summarized by DSM-5. The count and percentage of subjects under each DSM-5 code will be summarized using the safety population.

9.7 STATISTICAL CONSIDERATIONS

9.7.1 Statistical Approach

Analysis Populations: All baseline analysis will be performed using the mITT and Overall Safety Populations. All efficacy analysis will be performed using the mITT population. All safety analysis will use the defined safety populations as noted in section 9.5.

Descriptive Statistics: For descriptive statistics, the following will be reported:

- Continuous data: n, mean, standard deviation, median, interquartile range, minimum, and maximum
- Categorical: n/N and percent per arm

Missing Data: The mITT population, as defined, will ensure that all subjects will have at least one measurable post baseline time point. Missing data is anticipated to be minimal as this is a laboratory classroom study. Giving the primary purpose of the study, no additional explorations for missing data will be performed.

The planned analysis identified in the protocol and SAP will be included in the clinical study report (CSR). Any retrospective, ad-hoc, or exploratory analysis not defined in the SAP will be clearly identified in the clinical study report (CSR).

9.7.2 Primary Efficacy Endpoint Analysis

This primary purpose of this study is to obtain estimates of effect size. The planned model for the subsequent studies will be used in this study to understand the impact of covariates and model fit. However, it is not anticipated that significant treatment differences will be observed.

The primary efficacy endpoint is the treatment effect of the change from baseline in PERMP scores over the day during Visit 8. The PERMP aggregates the scores from all domains of the PERMP. The PERMP will be treated as a continuous measure. The primary efficacy analysis will analyse the mean change from Baseline (pre-dose) at Visit 8 and PERMP scores collected across the laboratory environment at Visit 8.

The estimate of the difference between CTx-1301 (active) and placebo will be analysed by using ANCOVA with treatment group as a fixed effect and baseline PERMP as a covariate.

The observed and change from Baseline PERMP will additionally be summarized at each applicable time point using the number of subjects, mean, standard deviation, median, minimum, and maximum values.

9.7.3 Key Secondary Efficacy Endpoint Analysis

Change from baseline at each time point will be analyzed using the same ANCOVA model, as described above.

The CGI-S will be the mean change from baseline (CGI-S at Visit 2) compared to Visit 8 (CGI-S).

No adjustments for multiple comparisons will be made in this study.

9.7.4 Exploratory Efficacy Endpoint Analysis

Descriptive statistics will be used to analyze any effect of treatment outcomes on the exploratory endpoints.

9.8 SAFETY

The safety data will be analyzed on the safety set. Safety endpoints include the occurrence of TEAEs, vital signs, BMI and weight, ECG results, and clinical lab test results.

Exposure to investigational product will be summarized.

Adverse events will be coded using the agreed upon version of the Medical Dictionary for Regulatory Activities.

The number of events, incidence, and percentage of TEAEs will be calculated overall, by System Organ Class (SOC), by preferred term, and by treatment group. TEAEs (including

severity/relationship) will be summarized by treatment and phase of study. TEAEs related to investigational products, AEs leading to withdrawal, SAEs, and deaths will be summarized.

Vital signs, ECG, weight, height, and BMI will be summarized by treatment and visit using the appropriate descriptive statistics.

9.9 INTERIM ANALYSIS

No interim analysis is planned.

10 ETHICAL AND REGULATORY ASPECTS

10.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The Principal Investigator will ensure that this study is conducted in full conformance with the laws and regulations of the country in which the research is conducted (FDA), as well as the Declaration of Helsinki 1964 and ICH GCP Guidelines

10.2 INFORMED CONSENT

It is the responsibility of the Investigator, or medically qualified designee, to obtain written (signed and dated) informed consent from each subject in this study. Major/substantial amendments to the protocol that affect the scope of the study at the subject level and/or updates to the safety profile of an investigational product will be reflected in the updated consent form and active subjects will be re-consented.

Eligible subjects may only be included in the study after written, IRB-approved informed consent, is obtained from the subject. Informed consent must be obtained prior to conducting any study-specific procedures (i.e., any procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

10.3 FDA

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

10.4 INDEPENDENT ETHICS COMMITTEE (IEC) / INSTITUTIONAL REVIEW BOARD (IRB)

This protocol (and any modifications) as well as appropriate consent procedures, will be reviewed and approved by an IEC/IRB. This body must operate in accordance with the current local requirements. A letter or certificate of approval must be received prior to initiation of the study, and also when subsequent, substantial modifications to the protocol are made.

If the study is stopped due to adverse events, it will not be recommenced without reference to the IEC/IRB responsible for the study.

The outcome of the study (e.g., completed) will be reported to the IEC/IRB responsible for the study within 90 days of completion of the last subject's final study procedures. In the

event of the study being prematurely terminated, a report will be submitted to the IEC/IRB responsible for the study within 15 days.

10.5 FUNDING

The study is funded by Cingulate Therapeutics, the Sponsor of the investigational study.

11 MONITORING OF THE STUDY

The extent and nature of monitoring will be described in a written monitoring plan held in the Trial Master File (TMF).

12 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

12.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into three categories: (1) Trial Master File (2) Regulatory file, and (3) study/subject clinical source documents (including eCRF). The site's regulatory file must be held at the study site for as long as needed to comply with national and international regulations. The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- IRB/IEC approvals for the study protocol and all amendments,
- All source documents and laboratory records,
- eCRF copies (electronic copies on a CDROM or USB/thumb drive),
- Subjects' informed consent forms (with study number and title of study),
- FDA form 1572,
- Any other pertinent study document.

12.2 SOURCE DOCUMENTS/DATA

The source documents (e.g., clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the eCRF, and source data recorded directly into the eCRF (e.g., inclusion/exclusion criteria, subject enrolment) should be specified in a source document designation form.

12.3 ELECTRONIC CASE REPORT FORMS

For each subject with documented informed consent, an eCRF must be completed and signed by the Principal Investigator to certify that the data are complete and correct. This also applies to those subjects who are screened but not entered into the study; data should be entered up to the point of screen failure. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be clearly made to document the outcome. An early termination eCRF must be completed for all early terminations; if early termination is due to an AE, it must be clearly noted that subject was terminated for an AE, specifying which AE required termination (if multiple AEs occur).

All eCRF pages should be completed during (or immediately after) a subject assessment.

The study monitor(s) will review all eCRFs and any queries will be highlighted to the Investigator, or designee(s), enabling the errors to be addressed prior to data lock of the eCRF pages.

12.4 CONTROLLED SUBSTANCE REGULATIONS AND LEGISLATION

When using controlled substances, the Investigator must comply with all local, state, and national laws pertaining to registration/reporting with the appropriate regulatory body and control/handling of such substances.

13 PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to the study, which could potentially adversely affect the safety of subjects, or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria must be made only after appropriate assessment of the issues involved.

All major/substantial protocol modifications/amendments must be reviewed and approved by the appropriate IEC/IRB. Approvals from the IEC/IRB must be received before the amended protocol can be implemented.

Modifications which eliminate an apparent immediate hazard to subjects do not require pre-approval by the IEC/IRB, but the IEC/IRB will be notified of these amendments.

Approval of amendments will be made by the original Investigator signatories to the protocol.

14 CONDITIONS FOR TERMINATING THE STUDY

The Sponsor reserves the right to terminate the study at any time.

In terminating the study, the Sponsor will assure that adequate consideration is given to the protection of the subject's interests. If the study is terminated prematurely or suspended, the IEC/IRB will be informed and provided with the reason(s) for termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirements.

15 CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that the anonymity of the subject is maintained. On eCRFs or other documents, subjects should not be identified by their names or initials, but by an identification code.

Data on subjects collected on eCRFs during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial subjects. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a subject participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

The Investigator should keep a separate log of subjects' codes and names. Documents which may identify the subject, e.g., subjects' written consent forms, will be maintained in strict confidence. Any electronic files that contain subjects' personal data will be appropriately encrypted. Any data sent to the sponsor must be redacted of all personal identifying information prior to sending.

16 AUDITS/INSPECTIONS

In addition to the routine monitoring procedures, the Sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of Good Clinical Practice.

The Investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

The Investigator and study subjects should understand that source documents for this study may be made available to appropriately qualified personnel for the study or designee(s) from FDA. The verification of the eCRF data may be by direct inspection of source documents (CRO and FDA) or through an interview exchange (FDA).

16.1 DISCLOSURE OF INFORMATION

All information provided to the Investigator by Cingulate Therapeutics, LLC, or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a written right of publication if granted to the Investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than to Cingulate Therapeutics or its authorized representatives, or in confidence to the IEC/IRB, or similar committee, except if required by law.

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