CLINICAL STUDY PROTOCOL

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTI-CENTER, FIXED-DOSE, PARALLEL GROUP EFFICACY AND SAFETY STUDY IN PEDIATRICS (6-17) WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) USING CTX-1301 (DEXMETHYLPHENIDATE)

Study Number: CTx-1301-005

Drug Development Phase:	Phase 3
Investigational Product:	Dexmethylphenidate
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
IND	136674
Lead Investigator:	[redacted]
Sponsor:	Cingulate Therapeutics [redacted]
Date:	Version 6, 13 Oct 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.

SUMMARY INFORMATION

Title:	A Phase 3, double-blind, randomized, placebo-controlled, multi-center, fixed-dose, parallel group efficacy and safety in pediatrics (6-17) with Attention-Deficit/Hyperactivity Disorder (ADHD) using CTx-1301 (dexmethylphenidate)
Protocol Number:	CTx-1301-005
Sponsor:	Cingulate Therapeutics
Primary Sponsor contact:	[redacted]
Secondary Sponsor contact:	[redacted]
Medical Monitor:	[redacted]

SPONSOR PROTOCOL APPROVAL

Protocol Title:	A Phase 3, double-blind, randomized, placebo-controlled, multi-center, fixed-dose, parallel-group efficacy, and safety study with CTx-1301 in pediatrics (6-17) with Attention-Deficit/Hyperactivity Disorder (ADHD) using CTx-1301 (dexmethylphenidate)
Protocol Number:	CTx-1301-005
Protocol Version:	6.0
Date of Version:	13 Oct 2023

Signed for approval by:

[redacted]

PROTOCOL SIGNATURE PAGE

I have read and understand the contents of this clinical protocol for Study No. CTx-1301-005 dated 13 OCT 2023 and agree to meet obligations of Cingulate Therapeutics as detailed in 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 stipulations, clinically and administratively, as stated in the protocol, including 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 necessary information required to conduct the study and that the study will not be initiated without the approval of an appropriate Institutional Review Board (IRB).

It is agreed that participants, parents/guardian, and caregiver (if applicable) in this study will provide written informed consent and assent in accordance with the requirements specified in the Declaration of Helsinki 1964. Participants will also be informed that their medical records will be kept confidential except for review by study site personnel and appropriate 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, 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.

Signed By:

Principal Investigator

_____

Date of Signature

_____

Emergency Contact Information

In the event of an SAE, the investigator must fax or e-mail the SAE Form within 24 hours to the [redacted] Pharmacovigilance Department. Applicable fax numbers and email address can be found on the SAE form. A copy of the SAE form must also be sent to the CRO/Medical Monitor by email using the following details.

For protocol or safety-related issues during normal business hours (8am-5pm) eastern standard time, the investigator must contact the [redacted] Medical Monitor:

[redacted]

Email Address: [redacted]

Please use the study identifier in the subject of your e-mail (and replies to e-mail); use the study-specific medical monitor e-mail and not individual e-mail addresses of medical monitors. The study e-mail address will distribute your e-mail automatically to back-up medical monitor(s), and ensure your e-mail will have a receiver, even if the lead medical monitor is out of the office. For urgent protocol or safety-related issues outside of normal business hours (8am-5pm) eastern standard time, the investigator must contact the [redacted] Medical Monitor:

Phone: [redacted]

This phone number will connect you to a call center and an operator will ask you for your details and will connect you through to a [redacted] medical monitor.

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STUDY SYNOPSIS

Title	A Phase 3, randomized, double-blind, placebo-controlled, multi-center, fixed-dose, parallel-group efficacy, and safety study in a pediatric population (6-17) with Attention-Deficit/Hyperactivity Disorder (ADHD) using CTx-1301 (d-MPH)
Sponsor	Cingulate Therapeutics
Short Title/Acronym	A Phase 3, Fixed-Dose, Pediatric Efficacy and Safety Study
Protocol Number	CTx-1301-005
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 Efficacy Study Period	Approximately 5 weeks (excluding screening)
Full Study Period	Approximately 10 weeks (including screening and safety follow up)
Objective(s)	**Primary objective:** • To evaluate the efficacy of a fixed dose of CTx-1301 compared to placebo in treating pediatric subjects with ADHD using the ADHD-RS-5 Total Score **Key Secondary objective:** • To evaluate the efficacy of a fixed dose of CTx-1301 compared to placebo in treating pediatric subjects with ADHD using the CGI-S score **Other Secondary objectives:** • To determine safety and tolerability of a fixed dose of CTx-1301 compared to placebo • To evaluate the PK levels of dexmethylphenidate after a single dose • To evaluate the PK levels of dexmethylphenidate at steady state • To evaluate the PK/PD correlation of dexmethylphenidate at steady state • To evaluate the CGI-I score at the end of treatment

Study Design and Methodology	A multi-center, double-blind, randomized, placebo-controlled, fixed-dose, parallel efficacy, and safety study with CTx-1301 in children (6-17) with ADHD confirmed by an ADHD-RS-5 score of at least 28 and CGI-S score of at least 4 (moderately ill) at baseline. The study will be comprised of a screening period, a double-blind randomized phase, and a safety follow-up visit. The Study will be comprised of 3 periods: • **Screening Period (Day -30 to Day -1):** Subjects will undergo a Screening Visit (Visit 1) up to 30 days prior to entering the randomized treatment period. Only subjects that meet inclusion and no exclusion criteria at screening may be considered for entry/randomization into the study. A reminder telephone call will be completed 5 days prior to Day 0 (Visit 2) to ensure washout of current prohibited medications, to confirm inclusion/exclusion criteria, and to confirm date of next visit. • **Randomized Treatment Period (Day 0 to Day 35 ± 3 days):** Subjects will be randomized on Day 0 to active or placebo (placebo, CTx-1301 18.75 mg, CTx-1301 25 mg, or CTx-1301 37.5 mg). Subjects randomized to the active dose will have a starting dose of 12.5 mg on Day 0. Each subject randomized to an active dose will be titrated (increased) weekly until they reach their assigned fixed dose; subjects must be on their assigned fixed dose a minimum of 2 sequential weeks prior to the primary efficacy assessment at Week 5/Visit 8. Subjects will be instructed to take their dose every morning at-home upon waking, no later than 8:00 am. • **Safety Follow-Up Phone Call (Day 42 ± 5 days):** Subjects will be evaluated for safety after washout of medication.
Number of Subjects/Number of Sites	Approximately 77 subjects per treatment group (CTx-1301 18.75 mg, 25 mg, 37.5 mg, and placebo) would provide 90% power at 2-sided significance level of 0.017 based on a two-sample t test with effect size 0.60 after Bonferroni correction (nQuery Version 8.4.1.0), which results in a total sample size of 308. Assuming a drop-out rate of 20%, approximately 385 subjects will be enrolled. The study will take place at approximately 25 sites in the United States.
Diagnosis and Main Inclusion Criteria	Healthy male and female subjects aged 6 to 17 years old, inclusive, diagnosed with ADHD and who are unsatisfied with their current pharmacological therapy for ADHD or are not currently receiving pharmacological therapy for ADHD will be entered into the study.

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: • 12.5 mg (starting dose only) • 18.75 mg (randomized fixed dose) • 25.0 mg (randomized fixed dose) • 37.5 mg (randomized fixed dose) CTx-1301 is a novel, trimodal, modified, 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. [redacted] The study drug should be administered at-home upon wakening in the morning, no later than 8:00 am, due to the extended efficacy of the investigational product. Dosing is one tablet per day. Study drug must be taken orally with approximately 240 mL (1 cup) of water. Study drug must be swallowed whole without any modification to the tablet (no crushing, chewing, or manipulating the tablet in any manner). Study drug may be taken with or without food (defined as food taken within one hour of study drug administration).
Reference therapy	The comparator product is a matching placebo tablet.
ADHD Severity/Efficacy Evaluation Criteria	The following scales will be used during the study to assess weekly the severity of ADHD as well as the eligibility of each subject: • ADHD-Rating Scale-5 (ADHD-RS-5) • Clinical Global Impression-Severity (CGI-S) • Clinical Global Impression-Improvement (CGI-I) • MINI International Neuropsychiatric Interview of Children and Adolescents (MINI-KID)
Safety Evaluation Criteria	Adverse events, vital signs, height, and weight (z-scores), sleep and appetite evaluation, physical examinations, ECGs, clinical laboratory measurements, and C-SSRS scores will be evaluated for safety.

Population PK and Sparse Sampling	Population PK analysis can be used to derive patient PK exposure metrics that can be used to conduct sequential exposure-response analyses. Population PK models can predict individual patient exposures at specific time points regardless of the spread in sampling times (e.g., trough concentrations can be predicted for subjects). Population PK analysis is especially appropriate in children because it allows the use of infrequent (i.e., sparse) sampling compared to the rich sampling associated with traditional PK analyses, thus minimizing the total volume of blood sampled. Sampling windows in pediatric studies are generally expected to be wider than those of adult studies, because of the limited number of blood samples obtained from pediatric patients. Sparse PK sampling will be conducted after a single dose and at steady state from the patient population with special attention given to the time the sample is obtained post-dose. These analyses will inform strategies that manage dosing and detail administration for a given subpopulation, planned subsequent studies, and support labeling.
PK Sampling	PK samples will be obtained on Day 1 (post-dose) and Week 5 (post-dose) recording the time the sample is obtained post-dose at each timepoint. Collection times at Day 1 (Visit 3) and Week 5 (Visit 8) will be 0.5 to 5 hours post-dose, 5-6.5 hours post-dose, and 6.5 to 8 hours post-dose. Collection times at Day 1 and Week 5 will be different for each subject (i.e., if assigned 0.5-5 hours post dose on Day 1, they will be assigned 5 to 6.5 hours or 6.5 to 8 hours post-dose at Week 5). Collection times will be assigned via automated IRT to ensure an approximately equal distribution among the 6 different combinations of timepoints. With 385 subjects at single dose (Day 1) and at least 308 subjects at Week 5, this should provide an adequate distribution to demonstrate Pop PK measurements.
Duration of Subject Participation and Duration of Study Treatment	Subjects will participate in the study as outpatients for up to approximately 10 weeks (including screening); a 30-day screening period, a 5-week double-blind randomized period, and a 1-week follow-up safety visit. Completion of the study will be defined as completion of the last subject, last visit (LSLV) at Visit 9. Subjects will be randomized at baseline to CTx-1301 or placebo (CTx-1301 18.75 mg, CTx-1301 25 mg, CTx-1301 37.5 mg, or placebo). Starting dose for subjects randomized to active treatment is 12.5 mg. These subjects will then be titrated up to their assigned fixed dose (18.75, 25, or 37.5 mg) for the last two weeks of the study period. Subjects randomized to placebo will receive placebo treatment for the full 5 weeks of the study.
Medication Restrictions	Subjects meeting eligibility requirements and enrolled into the study will be subject to medication restrictions during the trial:

	• ADHD stimulant medications (except for study drug CTx-1301), including herbal medications, are prohibited from 5 days prior to Baseline (Visit 2) and through the end of the study (Visit 9). These medications include, but are not limited to, methylphenidate and amphetamine isomers and prodrugs. • ADHD non-stimulant medications are prohibited from 21 days prior to Baseline (Visit 2) and through the end of the study (Visit 9). These medications include, but are not limited to atomoxetine, guanfacine, clonidine, SSRIs such as fluoxetine, paroxetine and viloxazine. • The following medications are prohibited from 21 days prior to Baseline (Visit 2) and through the end of the study (Visit 9) 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 / sedative antihistamines (e.g., hydroxyzime, Diphenhydramine (three brand names: Benadryl, Nytol, Sominex), sleep enhancers (except for melatonin) are prohibited from 14 days prior to Baseline (Visit 2) and through the end of the study (Visit 9) or early termination visit* • The Investigator, and CRO Medical Monitor, will evaluate the impact of the underlying medical reason, for cold or allergy antihistamines medications, taken on an as needed (ex. PRN use) frequency.

	**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 a maximum of 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 Baseline (Visit 2) and through the end of the study (Visit 9) or early termination visit. Medications allowed during 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 90 days prior to screening. Investigative site should attempt to obtain medical records for each subject.
Criteria for Pharmacokinetics Evaluation	The pharmacokinetic samples collected will be used to model and simulate the following pharmacokinetic parameters: Maximum Concentration (C_{max}), Time of Maximum Concentration (T_{max}), terminal elimination constant (K), lag time (T_{lag}), Half Life ($T_{1/2}$), Area Under the Curve from time 0 to 28 hrs (AUC_{last}), Area Under the Curve from time 0 to infinity ($AUC_{0-¥}$), and partial areas AUC_{0-3}, AUC_{3-6}, AUC_{3-7}, AUC_{6-9}, AUC_{7-12}, AUC_{9-12}, and AUC_{12-16}. Additional measures may be evaluated if deemed necessary.
Statistical Methods	
Analysis Populations	Intent-To-Treat (ITT) Population: Subjects who are randomized. Safety (SAF) Population: Subjects who have received at least one dose of study drug.

	Modified ITT (mITT) Population: Subjects in the ITT population and have at least one post-baseline ADHD-RS-5 assessment. Per Protocol (PP) Population: Subjects in the ITT population who have completed Baseline and Visit 8 efficacy assessments, demonstrate at least 80% medication compliance, and have no major protocol deviations that interfere with the primary efficacy analysis. The PP Population will be determined in a blinded manner prior to database lock.
Study Endpoints	Primary efficacy endpoint: change of the ADHD-RS-5 Total Score from Baseline (Visit 2) to Week 5 (Visit 8) Key secondary efficacy endpoint: change of the CGI-S Score from Baseline (Visit 2) to Week 5 (Visit 8) Safety endpoints: the occurrence of TEAEs, systolic and diastolic blood pressure, pulse, and weight, height, BMI, ECG, and C-SSRS PK endpoints: Maximum Concentration (C_{max}), Time of Maximum Concentration (T_{max}), terminal elimination constant (K), lag time (T_{lag}), Half Life ($T_{1/2}$), Area Under the Curve from time 0 to 28 hrs (AUC_{last}), Area Under the Curve from time 0 to infinity ($AUC_{0-¥}$), and partial areas AUC_{0-3}, AUC_{3-6}, AUC_{3-7}, AUC_{6-9}, AUC_{7-12}, AUC_{9-12}, and AUC_{12-16}. Additional measures may be evaluated if deemed necessary.
Efficacy Analyses	The hypotheses of the primary efficacy analysis will be the following: • Null hypothesis: There is no difference in the mean change of ADHD-RS-5 total scores from Baseline (Visit 2) to Week 5 (Visit 8) between CTx-1301 fixed doses (18.75, 25.0, 37.5 mg) and placebo. • Alternative hypothesis: There is a difference in the mean change of ADHD-RS-5 total scores from Baseline (Visit 2) to Week 5 (Visit 8) between any CTx-1301 fixed dose (18.75, 25.0, or 37.5 mg) and placebo. The primary efficacy analysis will be conducted in the ITT population using mixed-effects model for repeated measures (MMRM) with treatment group, visit, age group and the interaction of treatment group with visit as factors and Baseline ADHD-RS-5 Total Score as a covariate. Missing data will be imputed using multiple imputation. Sensitivity analysis will be conducted in the mITT and PP population if appropriate. The key secondary efficacy endpoint, CGI-S will be analyzed similarly as the primary efficacy endpoint using the same analysis method (MMRM). The Baseline CGI-S score will be used as the covariate. Missing data will be

	imputed using multiple imputation. Sensitivity analysis will be conducted in the mITT and PP population if appropriate. To protect the study-wide Type I error at the 2-sided 0.05 level for testing across multiple dosage groups on the primary endpoint (ADHD-RS-5 Total Score), Bonferroni correction is applied so that the hypothesis in each dose group is tested at alpha = 0.017. The subsequent key secondary endpoint (CGI-S) in each dose group will be analyzed following a hierarchical testing procedure. If the hypothesis is significant for the primary endpoint at the 2-sided 0.017 significance level, the key secondary endpoint will be analyzed. Both tests in the sequence are based on the MMRM.
Safety	Safety data will be summarized by treatment group and age group in the Safety population . Exposure to investigational product will be summarized. Adverse events will be coded using MedDRA. The number and percent of subjects with Treatment emergent AEs will be calculated for each system organ class, by preferred term, treatment group and age group. The severity of the TEAEs, the relationship to the investigational product, TEAEs causing study discontinuation, and serious AEs will also be summarized. Vital signs (systolic and diastolic blood pressure, and pulse), weight (z-scores), height, BMI, ECGs, clinical laboratory measurements, and C-SSRS results will be summarized by treatment and visit.
Pharmacokinetics	Pharmacokinetic parameters will be summarized descriptively by time collected, treatment group, and age groups as appropriate.

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-5	ADHD Rating Scale Version 5
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AV	Assessment Visit
BMI	Body Mass Index
bpm	Beats Per minute
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CS	Clinically Significant
C-SSRS	Columbia Suicide Severity Rating Scale
CTx	Cingulate Therapeutics
CTMS	Clinical Trial Management system
cm	Centimeters
d-MPH	Dexmethylphenidate
DA	Dopamine
DO	Dose Optimization
DMDD	Disruptive Mood Dysregulation Disorder
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 Response Technology
ITT	Intent-To-Treat
kg	Kilograms
L	Liter
LLN	Lower Limit of Normal
LSLV	Last Subject Last Visit
m	Meter
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
mL	Milliliter(s)
MMRM	Mixed-Effect Model Repeated Measure
mmHg	Millimeters of Mercury
MPH	Methylphenidate
MPV	Mean Platelet Volume
ms	Millisecond
mSv	Millisieverts
NCS	Not Clinically Significant
NMS	Neuroleptic Malignant Syndrome

NE	Norepinephrine
POC	Proof of Concept
PP	Per Protocol
PK	Pharmacokinetic
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**	**Washout Phone Call**	**Baseline**	**Day 1**	**Week 1 (± 3 days)**	**Week 2 (± 3 days)**	**Week 3 (± 3 days)**	**Week 4 (± 3 days)**	**Week 5[e] (± 3 days)**	**Week 6 Phone Call (± 5 days)**
Study Day	**-30 to -1 Days**	Day -5	0	1	7 (± 3 days)	14 (± 3 days)	21 (± 3 days)	28 (± 3 days)	35 (± 3 days)	42 (± 5 days)
Visit Number	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Parental Permission/ Written Assent	✓									
ADHD Diagnosis and Confirmation	✓[a]		✓[a]							
Tablet Swallowing 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	✓									
PK Blood Sampling				✓					✓	
Serum hCG[f]	✓								✓	
Urine hCG[fg]			✓		✓	✓	✓	✓	✓	
TSH	✓									
Urine Screen for Methylphenidate	✓		✓							

Procedure / Assessments	**Screening/ Washout**	**Washout Phone Call**	**Baseline**	**Day 1**	**Week 1 (± 3 days)**	**Week 2 (± 3 days)**	**Week 3 (± 3 days)**	**Week 4 (± 3 days)**	**Week 5[e] (± 3 days)**	**Week 6 Phone Call (± 5 days)**
Study Day	**-30 to -1 Days**	Day -5	0	1	7 (± 3 days)	14 (± 3 days)	21 (± 3 days)	28 (± 3 days)	35 (± 3 days)	43 (± 5 days)
Visit Number	**1**	**N/A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Urine Screen for Drugs of Abuse	✓		✓						✓	
C-SSRS Screening[h]	✓									
C-SSRS[h] (Since Last Visit)			✓		✓	✓	✓	✓	✓	
MINI-KID	✓									
ADHD-RS-5[a]	✓[a]		✓[a]		✓	✓	✓	✓	✓	
CGI-S[a]	✓[a]		✓[a]		✓	✓	✓	✓	✓	
CGI-I									✓	
Prior Medication Questionnaire			✓							
AE Assessment[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization			✓							
Dispense Double-Blind Study Drug Administration			✓		✓	✓	✓	✓		
Drug Accountability & Compliance Assessment				✓	✓	✓	✓	✓	✓	
Collect/Distribute Dosing Diary			✓	✓	✓	✓	✓	✓	✓	
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Study Completion/Medical Sign-Off									✓	

a. Subjects must meet inclusion criteria prior to randomization at Baseline/Visit 2. The Eligibility/Baseline ADHD-RS-5, and CGI-S must be assessed after appropriate washout from ADHD medications (stimulants and non-stimulants). If able to complete at Screening Visit, these assessments do not need to be repeated at Visit 2. If unable to complete at Screening Visit due to washout requirement, this may be taken at Visit 2.
b. Height and weight will be measured without shoes and with light clothing using a calibrated stadiometer and scale.
c. The Eligibility/Baseline ECG must be assessed after appropriate washout from ADHD medications (stimulants and non-stimulants). If able to complete at Screening Visit, these assessments do not need to be repeated at Visit 2. If unable to complete at Screening Visit due to washout requirement, this may be taken at Visit 2.
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. Early Termination Visits should follow the Visit 8/Week 5 visit study assessment schedule.
f. Females of childbearing potential.
g. 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.
h. 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]

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. [redacted]

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.

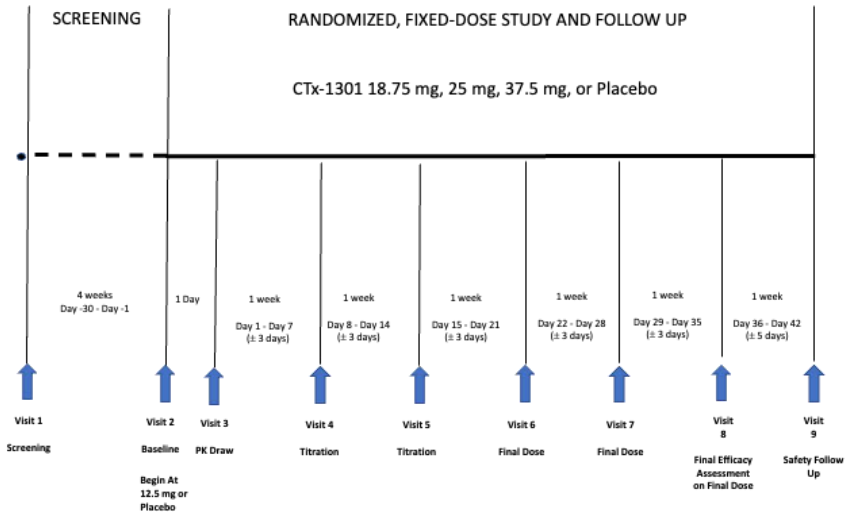
1.2 OVERVIEW OF CLINICAL STUDIES WITH CTX-1301

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, Focalin XR®, to CTx-1301, and to determine the gastrointestinal transit parameters of CTx-1301. Each subject received one dose of 10 mg Focalin XR®, (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). [redacted]

The sponsor also conducted CTx-1301-001, the pivotal comparative BA study, which demonstrated bridging to the LD (Focalin XR®,) and allows reliance on the previous findings of the LD for safety. The comparative BA study evaluated the lowest dose of Focalin XR®, (5 mg) to the lowest dose of CTx-1301 (6.25 mg) and the highest dose of Focalin XR®, (40 mg) to the highest dose of CTx-1301 (50.0 mg). This study was completed with 39 ADHD patients and each patient received 4 doses. The primary objectives of this study were to compare the bioavailability of the listed drug, Focalin XR®, 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. [redacted]

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 a fixed dose of CTx-1301 for treatment of ADHD in a pediatric population including children ages 6-17 years. 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 three fixed doses over 5 weeks.

2.3 PRIMARY OBJECTIVE

- To evaluate the efficacy of three fixed doses of CTx-1301 compared to placebo in treating pediatric patients with ADHD utilizing the ADHD-RS-5.

2.4 SECONDARY OBJECTIVE(S)

- To evaluate the efficacy of a fixed dose of CTx-1301 compared to placebo in treating pediatric patients with ADHD utilizing the CGI-S.
- To determine safety and tolerability of a fixed dose of CTx-1301 compared to placebo
- To evaluate the PK levels of dexmethylphenidate after a single dose
- To evaluate the PK levels of dexmethylphenidate at steady state
- To evaluate the PK/PD correlation of dexmethylphenidate at steady state
- To evaluate the CGI-I score at the end of treatment

3 INVESTIGATIONAL PLAN AND DESIGN

3.1 STUDY DESIGN

The study design is a double-blind, randomized, placebo-controlled, fixed-dose, parallel-group efficacy, and safety study with CTx-1301 in children (6-17) with ADHD confirmed by an ADHD-RS-5 score of at least 28 at baseline. The study will be comprised of a 30-day screening period, a 5-week randomized period, and a 1-week safety follow-up period.

The Study will be comprised of 3 periods:

- Screening Period (Day -30 to Day -1): Subjects will undergo a Screening Visit (Visit 1) up to 30 days prior to entering the 5-week randomization period. Only subjects that meet inclusion and no exclusion criteria at screening may be considered for enrollment in the randomized portion of the study.

- Double-Blind Randomized Period (Day 0 - Day 35 ± 3 days): During the 5-week randomized period (Visits 2-8), subjects will have weekly visits to assess safety and efficacy. Eligible subjects will be randomized at Visit 2. Subjects randomized to active will have a starting dose of 12.5 mg and will be titrated up (increased) to their assigned fixed dose of CTx-1301 (18.75, 25, or 37.5 mg); subjects randomized to placebo will receive placebo throughout the entire randomized period. Each subject is required to be on their assigned fixed dose a minimum of 2 sequential weeks prior to the final efficacy assessment at Visit 8 (Week 5).

- Safety Follow-Up Phone Call (Days 36 - Day 42 ± 5 days): Subjects will washout after the efficacy assessment at Visit 8 and have a follow-up phone call (Visit 9) to ensure safety of subjects.

3.2 RATIONALE FOR STUDY DESIGN

The purpose of this study is to evaluate the safety and efficacy of a fixed dose of CTx-1301 in a pediatric population (6-17) in randomized, double-blind, fixed-dose study using the ADHD-RS-5.

Dose selection was chosen to obtain safety and efficacy data across the range of doses (low, medium, and highest proposed dose for the age groups). Given traditional dosing regimens for dexmethylphenidate, the randomized active doses selected (18.75 mg, 25 mg, and 37.5 mg) will be the best range for the treatment groups (with a lead-in dose of 12.5 mg for active arms). Equivalent doses are being used in clinical practice to treat children and adolescents.

The lead-in dose of 12.5 mg for active arms is considered safe and tolerable in the selected patient population due its release profile [redacted]

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 school and medical referrals if required.

Assuming a dropout rate of 20%, 385 subjects will be required to enter the randomized period of the study to achieve the target of approximately 308 subjects (154 in each subgroup) to complete the study (approximately 77 per treatment arm in each subgroup).

4.2 CRITERIA FOR EVALUATION

Eligibility of subjects for study enrollment will be based on the results of a Screening medical history, tablet swallowing test, physical examination, mental state examinations, vital signs (blood pressure and pulse), the inclusion/exclusion criteria as described below, and clinical laboratory tests. 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 at screening and any pre-existing conditions will be documented as medical history.

4.3 INCLUSION CRITERIA

1. Male or female subjects between 6 and 17 years of age (inclusive) at the time of Randomization (Visit 2). Subjects who are expected to turn 18 years of age during the trial will not be allowed.
2. Subject must have a body weight between the 5th and 95th percentile (≥5th percentile and ≤95th percentile) for their respective age and sex.
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. Subjects of child-bearing potential at screening or that become of child-bearing potential during the study must agree to remain abstinent or agree to use a highly effective, medically acceptable form of birth control for the time of written assent and for at least 30 days after the last dose of study drug has been taken (females). 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. Child-bearing potential is defined as any female who has had their first period or is 12 years or older (or will be 12 while in the study).
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 (QTc less than or equal to 460 milliseconds), 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. Subject must meet Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria for the primary diagnosis of ADHD or any of the three presentations (combined, inattentive, or hyperactive/impulsive presentation) upon clinical evaluation and confirmed by the MINI International Neuropsychiatric Interview of Children and Adolescents (MINI-KID). The MINI should also be used to evaluate any other psychotic disorders.
8. Subject must score 28 or higher on the ADHD-RS-5 scale at the Baseline visit (Visit 2).
9. Subject must have a score of 4 (moderately ill) or higher on the clinician-administrated Clinical Global Impressions-Severity (CGI-S) scale at Baseline (Visit 2).
10. Subject must be able and willing to wash out of stimulant ADHD medications (except study drug as indicated per protocol), including herbal medication, from 5 days prior to the start of the randomized phase (Visit 2) and for the duration of the entire study, defined as completion of the safety follow-up visit (approximately 1.25 months, excluding screening). Additionally, subject must be able and willing to wash out from non-stimulant ADHD medications 21 days prior to the start of the randomized phase (Visit 2) and for the duration of the entire study (approximately 1.25 months, excluding screening), defined as completion of the safety follow-up visit.
11. Subject and parent/legal guardian, and/or caregiver (if applicable) 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 and parent/legal guardian, and/or caregiver (if applicable) must plan to be available for the entire duration of the study.
12. One or more of the parents/legal guardians/caregivers of the subject must voluntarily give written permission for him/her to participate in the study.
13. Subject must provide written assent prior to study participation.
14. Subject, subject's parent/legal guardian, and/or caregiver (if applicable) must understand and be willing and able to comply with study procedures as well as the visit schedule. If the subject is cared for by a caregiver for relevant portions of the day, the caregiver may be more suitable for certain assessments, and the caregiver will need to agree to the applicable procedures and visits.
15. Subject must be able to swallow the CTx-1301 tablet as evidenced by ability to swallow a similar size tablet (placebo) at screening.

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, defined as completion of safety visit at the end of study (Visit 9). 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, major depressive disorder, conduct disorder, disruptive mood dysregulation disorder (DMDD), intellectual disability, obsessive-compulsive disorder, eating disorder, anxiety disorder (including generalized anxiety disorder), any history of psychosis, autism spectrum disorder, a

history of motor or vocal tics or 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/uncontrolled medical abnormality or 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 of any lifetime history on the C-SSRS Children's 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. If the subject's blood pressure is < 90th percentile for their age, sex, and height, the single read is sufficient. If the subject's blood pressure is ≥ 90th percentile, two additional reads will be taken, and the three reads will be averaged. If the average of the three readings is ≥ 95th percentile at screening they will be excluded.
10. Subject is considered treatment refractory by the Investigator or is intolerant to stimulant ADHD mediation.
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 use or has a positive 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. Previous treatment experience/exposure to CTx-1301.
16. Subject has a history of allergic reaction or sensitivity to methylphenidate, dexmethylphenidate, or any other substance contained in CTx-1301 or the placebo drug.
17. Subject has participated in any other clinical study with an investigational drug/product within 30 days prior to Screening or is currently participating in another clinical study.
18. Subject's family 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.

19. Subject is unsuitable in any other way, to participate in the study, as determined by the Investigator.
20. Subject is a family member of an employee 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.

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 those 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, 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 attempted at the time of withdrawal including an explanation of why the subject is withdrawing from the study. The early termination visit should follow the Visit 8 schedule of events along with a final ECG.

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 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 and is not related to non-qualifying ADHD-RS-5 or CGI-S score at Baseline Visit (Visit 2). 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 rescreened 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. Drop-outs will not be replaced.

4.7 TREATMENT AND SUBJECT RESTRICTIONS

4.7.1 MEDICATIONS AND TREATMENTS

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

- ADHD stimulant medications (except for study drug), including herbal medications, are prohibited from 5 days prior to Visit 2 to the end of the study (Visit 9) or early termination visit. These include but are not limited to methylphenidate and amphetamine isomers and prodrugs.

- ADHD non-stimulant medications are prohibited from 21 days prior to Visit 2 to the end of the study (Visit 9) or early termination visit. These include, but are not limited to, atomoxetine, guanfacine, clonidine, and SSRIs such as fluoxetine and paroxetine.

- The following medications are prohibited from 21 days prior to Visit 2 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 / sedative antihistamines (e.g., hydroxyzime, Diphenhydramine (three brand names: Benadryl, Nytol, Sominex), sleep enhancers (except for melatonin) are prohibited from 14 days prior to Baseline (Visit 2) and through the end of the study (Visit 9) or early termination visit*

- The Investigator, and CRO Medical Monitor, will evaluate the impact of the underlying medical reason, for cold or allergy antihistamines medications, taken on an as needed (ex. PRN use) frequency.

**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 Visit 2 to the end of the study (Visit 9) or early termination visit.

4.7.2 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.

4.7.3 PROTOCOL DEVIATIONS

Subjects, parent/legal guardians, and/or caregivers (if applicable) will be questioned on compliance with restrictions during Screening, 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. Deviations should be documented in the appropriate database such as a Clinical Trial Management system (CTMS).

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:

- 12.5 mg (titration only)
- 18.75 mg (randomized fixed dose)
- 25.0 mg (randomized fixed dose)
- 37.5 mg (randomized fixed dose)

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. [redacted]

5.1.2 SELECTION OF DOSES

Subjects will be randomized to active or placebo drug by the IRT according to the subject randomization created by the unblinded statistician that was imported into the IRT. Those subjects that are assigned to active drug will be titrated to a randomly assigned fixed dose by the IRT; subjects' starting dose on active drug will begin with 12.5 mg and will titrate up weekly to one of three possible fixed dose drug levels 18.75 mg, 25 mg, or 37.5 mg. Each subject is expected to stay on their assigned fixed dose for at least 2 sequential weeks prior to Week 5 (Visit 8).

Possible assigned fixed doses are: 18.75, 25.0, 37.5 mg of CTx-1301, or placebo.

5.1.3 ADMINISTRATION

Under supervision from the subject's parent/legal guardian, and/or caregiver (if applicable), subject will self-administer the study drug daily on an outpatient basis for the full duration of the study, beginning on the day after Visit 2 and ending at Visit 8; between Visit 8 and Visit 9, a washout of study drug is required.

- Study drug (1 tablet per day) should be taken orally, upon wakening, at approximately the same time each day, and prior to 8:00 am.

- Study drug may be taken with or without food. For the purpose of this study, taken with food will be described as food taken within one hour of study drug administration.

- Study drug 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.).

If a subject forgets to take a dose prior to 8:00 am, the subject should skip the dose and resume taking the medication the following day. 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.

5.1.4 DOSE SCHEDULE

It is recommended that dosing takes place upon wakening, and no later than 8:00 am in the morning due to the extended efficacy of the investigational product. Subject should take dose for entire randomized efficacy assessment period (Visit 2 through Visit 8).

5.1.5 DOSE MODIFICATION

No alteration of the tablet is allowed (crushing, chewing, dividing, etc.) at any time during the study. Subjects will be randomized on Day 0 to active or placebo (placebo, CTx-1301 18.75 mg, CTx-1301 25 mg, or CTx-1301 37.5 mg). Subjects randomized to the active dose will have a starting dose of 12.5 mg on Day 0. Each subject randomized to an active dose, will be titrated up to their randomly assigned fixed dose at weekly increasing dose intervals by the IRT until they reach their assigned fixed dose (example titration increase possibilities: 12 to 18.75 mg, or 12 to 18.75 to 25 mg, or 12 to 18.75 to 25 to 37.5 mg); subjects must be on their assigned fixed dose for a minimum of 2 sequential weeks prior to the primary efficacy assessment at Week 5/Visit 8. Subjects will be instructed to take their dose every morning at-home upon waking, no later than 8:00 am.

5.1.6 TREATMENT COMPLIANCE

Subjects must agree to take the study medication daily at-home as detailed per the protocol. Subjects and their parents/legal guardians, and/or caregivers (if applicable) will be instructed to complete at-home dosing diary entry with each dose and bring diary with them to each visit.

Compliance with the study drug will be monitored and determined at each visit. Subjects and their parent/legal guardian, and/or caregiver (if applicable) will be instructed to bring unused study drug with them to each visit. 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 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 Sponsor or Sponsor's designee (i.e., Medical Monitor). Noncompliance issues will be discussed with the subjects and their parent/legal guardian, and/or caregiver (if applicable) and at the Investigator's discretion, may result in termination from the study. Subjects and their parent/legal guardian, and/or caregiver (if applicable) 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.

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., 37.5 mg. Notifications of subjects taking more than one tablet of study drug per day (irrespective of dose size) will be provided by each 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 (Focalin XR® 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 have been included to minimize possible risks in relation to administration of CTx-1301 (d-MPH).

The most common adverse reactions after taking d-MPH (Focalin XR®) 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 Focalin XR®.

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

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

	Focalin XR N=53	Placebo N=47
No. of Patients with AEs		
Total	76%	57%
Primary System Organ Class/ Adverse Event Preferred Term		
Gastrointestinal Disorders	38%	19%
Dyspepsia	8%	4%
Metabolism and Nutrition Disorders	34%	11%
Decreased Appetite	30%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

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 Focalin XR® Extended-Release Package Insert.

5.2 STUDY TREATMENT ASSIGNMENT

Subjects randomized to active treatment will have a starting dose of 12.5 mg; they will then be titrated up to their assigned fixed dose (18.75 mg, 25 mg, or 37.5 mg) by the IRT . An IRT system will be used to track each subject's dose of drug during the titration phase as well as track that they are on their assigned fixed dose for the last 2 weeks of the randomized efficacy period.

Treatment (active or placebo), given to individual subjects during the double-blind, randomized, efficacy period of the study, is determined by a randomization schedule; the randomization schedule will randomly assign eligible subjects to 1 of 4 treatment groups (A, B, C, or D) and be in an allocation ratio of 1:1:1:1 (active 18.75 mg: active 25 mg: active 37.5 mg: placebo). The actual treatment assigned to each subject is executed by an IRT system utilizing the randomization schedule. Subjects will be stratified by age groups (6-12) and (13-17). Investigational products (active and placebo) will appear identical to ensure blinding.

5.2.1 ENROLLMENT PROCEDURE

Subjects who meet inclusion and none of the exclusion criteria at Screening and at Baseline (Visit 2) may be enrolled into the double-blind, randomized study. Subjects will be randomized via IRT to active or placebo 1:1:1:1 stratified by each age group (6-12 and 13-17) at Visit 2.

5.2.2 BLINDING PROCEDURE AND CODE BREAKS

Study drug (CTx-1301 and placebo) is identical in color, shape, size, and packaging to maintain the blind.

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 except for the unblinded Biostatistician and the Clinical Trials Material Management Personnel

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

If breaking of 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 via the Emergency Unblinding Authorization Form
- 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

Please refer to CRO unblinding procedure.

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.

Questions can be directed to the [redacted] Customer Care Team at:

[redacted]

Or

[redacted]

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) if the excursion does not exceed 24 hours; excursions exceeding 24 hours must be reported immediately to the CRO. Deviations from the storage requirements must be documented and reported to the CRO and Sponsor. 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 investigational drugs per CFR 21 Subpart A, Section 312.6.

5.3.3 ACCOUNTABILITY OF STUDY SUPPLIES

Enough 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. IP must be accounted for via documentation that accurately records IP that is received, dispensed, administered, returned to site, and returned to Sponsor (or Sponsor 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 designated parent/legal guardian, and/or caregiver (if applicable) of the subject. Subjects will receive enough IP to last them until the next in-clinic visit. Subjects must return 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 local, state, and national laws regarding shipment of Scheduled II Controlled Substances.

At the end of the study, or as instructed by the Sponsor, unused stock, subject-returned IP, and empty/used IP packaging 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 CRO). 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 contractor should be contacted for authorization to return any IP. Shipment of 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

Study drug 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) if the excursion does not exceed 24 hours; excursions exceeding 24 hours must be reported immediately to the CRO. Deviations from the storage requirements must be documented and reported to the CRO and Sponsor. 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 PARENTAL PERMISSION AND INFORMED CONSENT

The Investigator, or designated study staff, must obtain written (signed and dated) parental permission and informed consent from the parent/legal guardian, and/or caregiver (if applicable) 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. There must also be written (signed and dated) assent indication that the subject is aware of the investigational nature of the study, and the required procedures and restrictions, prior to the performance of any study-related procedures.

The Investigator, or designated study staff, must also explain to the subjects, parent/legal guardian, and/or caregiver (if applicable) 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 and assent must be obtained prior to any study procedures being conducted. The Investigator,

or designated study staff, should sign and date the consent and assent form to confirm that the consent process was completed correctly and the subject, parent/legal guardian, and/or caregiver (if applicable) has fully understood the objectives of the study as well as the risks.

The subject, legal guardian, and/or caregiver (if applicable) will be provided with a copy of their signed and dated consent and assent 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 participation in the trial, any new information becomes available that may affect the subjects, parent/legal guardians, and/or caregivers (if applicable) 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, parent/legal guardians, and/or caregivers (if applicable) should be provided with a copy of the signed and dated amended consent and assent 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 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 of Children and Adolescents (MINI-KID). In addition, the subject must score 28 or higher on the ADHD-RS-5 scale and a 4 or higher on the clinician-administrated Clinical Global Impressions-Severity (CGI-S) scale at the Baseline Visit (Visit 2).

Subjects must have adequate washout of ADHD medications prior to Visit 2. See inclusion/exclusion criteria for washout information (section 4.2).

6.3 DEMOGRAPHICS

The Investigator, or designee, will record each subject's date of birth, sex (at birth), 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. 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

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 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, parents/legal guardians, and/or caregivers (if applicable), will be asked about prior medical history and response utilizing stimulant medications (including sleep and appetite evaluation) at the Baseline Visit 2.

6.7 PHYSICAL AND NEUROLOGICAL EXAMINATIONS

The investigator, or medically qualified designee, will perform the physical examination at the protocol specified times, which will include assessments 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
- Hematopoietic/lymphatic
- Endocrine/metabolic

The outcome of these assessments will be documented in the source. Pre-treatment findings or clinically significant abnormalities should be noted as medical history and post treatment findings or clinically significant abnormalities should be added as adverse events. Abnormalities should 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.

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

Body weight and height will be recorded at the protocol-specified times within the Vital Signs eCRF. Weight will be measured in kilograms (kg) while wearing light clothing and without shoes. Weight measurements should be taken with the same calibrated scale and recorded to the nearest tenth of a kilogram. Subject must have a body weight between the 5th and 95th percentile (≥5th percentile and ≤95th percentile) for their respective age and sex at screening to be eligible.

Height will be measured in centimeters (cm) without shoes. 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.

6.9 VITAL SIGNS

Arterial blood pressure, heart rate, and temperature will be recorded at screening and 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. If the subject's blood pressure is <90th percentile for their age, sex, and height, the single read is sufficient. If the subject's blood pressure is ≥90th percentile, two additional reads will be taken, and the three reads averaged. If the average of the three reads is ≥95th percentile at screening they will be excluded. If the average of the three reads is ≥95th percentile after screening, it will be recorded as an AE. 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[29,30] 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.

6.10 TABLET SWALLOWING TEST

The subject will be administered a tablet (placebo) identical in size and shape to the study drug at screening to ensure the subject is able to easily swallow CTx-1301 for the duration of the study.

6.11 CLINICAL LABORATORY TESTS

The Investigator, or appropriately trained study staff, will collect blood samples at screening for: serology, TSH, hematology, biochemistry, and a urine sample for urinalysis, and at Visit 8 (or early termination) for: hematology, biochemistry, and urinalysis. Values for the laboratory safety tests (hematology, biochemistry, and urinalysis) must be within normal ranges, as defined by the accredited central laboratory facility, or considered not clinically significant by the Investigator at screening to be eligible. The results of these tests must be available before subjects are enrolled into the randomization 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.

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 Visit 8 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).

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, urobilinogen, ketones, glucose, proteins, blood, nitrite, pH, specific gravity, and leukocytes.

Urine Screen for Drugs of Abuse

At Screening (Visit 1), Baseline (Visit 2), and Week 5 (Visit 8) urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and opioids) per the study schedule (see Table 1).

Urine samples will be tested for methylphenidate at screening and Day 0 Baseline (Visit 2).

If the urine test is positive for drugs of abuse at Screening or Baseline (Visit 2), the subject must be excluded from study participation, except for the subject's current ADHD medication (at Screening only). Subjects are required to washout of their ADHD medications prior to Baseline (Visit 2).

The Investigator, in conjunction with the Sponsor and CRO Medical Monitor, will evaluate the potential impact of a positive urine drug screen on the continued participation of the subject.

Pregnancy Test

Pregnancy tests will be performed for female subjects of childbearing potential. A serum hCG pregnancy test will be performed at Visit 1 and Visit 8 (or early termination visit). A urine hCG will be performed at Visits 2, and 4-8 per the study schedule (see Table 1). 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.

"Childbearing potential" is defined as females under the age of 12 who have had their first period. Girls 12 years and older (including girls who will become 12 years or older during the study) will be considered of child-bearing potential, even if they have not had their first period. Irrespective of age, girls who have had their first period will be considered of child-bearing potential.

6.12 PHARMACOKINETIC BLOOD SAMPLING

At Day 1 (Visit 3) and Week 5 (Visit 8) a single blood sample for pharmacokinetic (PK) assessment will be drawn by suitably trained site staff using an indwelling cannula or by venipuncture. The Week 5 PK draw will be combined with the safety lab draw at Week 5 to avoid separate draw.

The total blood volume taken for each blood sample will be approximately 5 mL per visit (4 mL sample volume and 1 mL of waste volume). The time of PK draw should be recorded at each of the two visits. Accordingly, if subject does not take dose the day of the PK draw, the PK draw should not be completed, and it should be recorded in the CRFs.

There is a risk of bruising and fainting during the blood sampling procedure. See AE section for reporting procedure-related AEs.

The PK blood samples should be collected in vacutainers containing K2-EDTA as the anticoagulant. Each blood tube will be labelled with the Subject Number and time collected post dose (ex. 3 hours post dose). Blood samples should be kept in ice/water bath until centrifugation. Blood samples should be centrifuged at 1,500 g for 10 minutes at 4°C if a refrigerated centrifuge is available or non-refrigerated centrifuge can be used within 60 minutes of collection. A minimum of 0.5 mL plasma should be aliquoted into two polypropylene tubes (Primary and Backup); if there is not sufficient plasma for both, preference should be given to the Primary sample. Each plasma sample should be kept in an ice/water bath environment until storage. Each plasma sample must be stored at -20ºC nominal within 30 min of centrifuging.

The analysis of these samples will be undertaken by a Sponsor-selected laboratory. Blood samples for PK determination will be processed, split, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility. Samples will be evaluated using a validated d-MPH method.

The pharmacokinetic samples collected will be used to model and simulate the following pharmacokinetic parameters by population PK:

Maximum Concentration (C_{max}), Time of Maximum Concentration (T_{max}), terminal elimination constant (K), lag time (T_{lag}), Half Life ($T_{1/2}$), Area Under the Curve from time 0 to 28 hrs (AUC_{last}), Area Under the Curve from time 0 to infinity ($AUC_{0-¥}$), and partial areas AUC_{0-3}, AUC_{3-6}, AUC_{3-7}, AUC_{6-9}, AUC_{7-12}, AUC_{9-12}, and AUC_{12-16}. Additional measures may be evaluated if deemed necessary.

Collection times at Day 1 (Visit 3) and Week 5 (Visit 8) will be 0.5 to 5 hours post-dose, 5-6.5 hours post-dose, and 6.5 to 8 hours post-dose. Collection times at Day 1 and Week 5 will be different for each subject (i.e., if assigned 0.5-5 hours post dose on Day 1, they will be assigned 5 to 6.5 hours or 6.5 to 8 hours post-dose at Week 5). Collection times will be assigned via automated IRT to ensure an approximately equal distribution among the 6 different combinations of timepoints. With approximately 385 subjects at Day 1 and at least 308 subjects at Week 5, this should provide an adequate distribution to demonstrate Pop PK measurements.

6.13 ECG

ECGs will be administered at Visit 1 and Visit 8 (or early termination visit). Visit 1 ECGs should be obtained when subject is not on ADHD medication and may be taken at Visit 2 if needed. ECGs will be recorded in triplicate and will be collected after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip and will be collected using recorder provided by the central ECG vendor/reader. ECGs should be recorded prior to drawing blood samples (if applicable to visit). Typical length between triplicate tracings is usually between 5 and 10 minutes.

The initial read of the ECGs will be done immediately by the Investigator after collection to ensure the safety of subjects. The ECG tracings will be sent electronically to the central reader for analysis. The Investigator must review the central ECG provider report. If abnormal and significant results are observed following analysis by the central reader, the Investigator, in consultation with the CRO Medical Monitor, will reconfirm subject eligibility to continue.

The central read will determine the eligibility of subjects for enrollment into the study (Visit 1). A final read for safety will occur at Visit 8. If a subject early terminates for any reason, an ECG should be conducted along with the other study procedures for Visit 8.

The 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.

6.14 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 scale takes approximately 5 minutes to administer. 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) will be completed; for 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 during the study must be referred to the Investigator for assessment. If investigator defines as significant, the medical monitor should also be notified (through CRO email). Any potential subject deemed to be at risk will be excluded from the study.

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

6.15 STUDY EVALUATIONS AND EFFICACY ASSESSMENTS

Rating scales and assessments completed for each individual subject, including the ADHD-RS-5, CGI-S, CGI-I and MINI-KID should be completed by the same Investigator (or appropriate designee) and parent/legal guardian, and/or caregiver (if applicable) whenever possible. Clinicians who administer these scales and/or assessments will be trained, experienced with the scale/assessment, and approved by the Sponsor prior to administration.

6.15.1 ADHD-RS-5

The ADHD-RS-5 is an 18-item scale based on Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association 2013) criteria of ADHD that rates symptoms on a 4-point scale. Each item is scored using a combination of severity and frequency ratings from a range of 0 (reflecting no symptoms or a frequency of never or rarely) to 3 (reflecting severe symptoms or a frequency of very often), so that the total ADHD-RS-5 scores range from 0 to 54. The 18 items can be divided into two 9-item subscales: One for hyperactivity/impulsivity and the other for inattentiveness. Scores will be obtained during a clinician-directed interview with the parent/legal guardian, and/or caregiver (if applicable) at each visit. The ADHD-RS-5 will be completed at every in-office visit or early termination visit, if applicable. The ADHD-RS-5 at the Baseline visit requires adequate washout of medication.

6.15.2 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 2, 4-8 or early termination visit, if applicable. CGI-S at the Baseline visit requires adequate washout of medication.

6.15.3 CGI-I

The CGI-I is a clinician-rated scale that is scored from 1 (very much improved) to 7 (very much worse). The CGI-I will be completed at Visit 8.

6.15.4 MINI-KID

The MINI International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) 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 for multicenter clinical trials. The interview takes approximately 30 minutes to administer. The MINI-KID will be administered by a trained clinician at the site.

The MINI-KID will be administered at Screening to confirm the diagnosis of ADHD in conjunction with the ADHD-RS-5 and CGI-S at the Baseline Visit (Visit 2). 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.

6.16 DESCRIPTION OF OTHER STUDY PROCEDURES

6.16.1 DRUG ACCOUNTABILITY AND COMPLIANCE

Compliance with the study drug will be monitored and determined at each in-office visit. Subjects and their parent/legal guardian, and/or caregiver (if applicable) will be instructed to bring unused study drug and used/empty packaging with them to each visit. 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 their parent/legal guardian, and/or caregiver (if applicable), and at the Investigator's discretion, may result in termination from the study. Subjects and their parent/legal guardian, and/or caregiver (if applicable) 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.

6.16.2 BLOOD SAMPLING

Blood samples for safety will be taken at Screening for eligibility, and again at Week 5 (Visit 8). Blood sample for pharmacokinetic assessments will be taken post-dose at Day 1 (Visit 3) and post-dose at Week 5 (Visit 8). There is a risk of bruising and fainting during blood sampling.

6.16.3 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 Visit 9 (as defined previously), the Investigator will perform a medical sign-off for each subject.

6.17 DURATION OF THE STUDY

Subjects will participate in the study as outpatients for approximately 10 weeks: a 30-day screening period, a 5-week, randomized, double-blind treatment period, and a 1-week follow-up safety assessment visit (if applicable).

Completion of the study will be defined as completion of the last subject, last visit (LSLV) at Visit 8 [redacted].

The treatment duration is approximately 5 weeks.

Subjects will receive a single, daily dose of CTx-1301 during the 5-week, double-blind, randomized, efficacy period of the study.

7 STUDY SCHEDULE

7.1 SCREENING (DAYS -30 TO -1)

After obtaining parental informed consent and child assent, subjects will be evaluated at their Screening Visit to determine whether they are eligible to enroll into the study. Subjects who are adequately washed out of ADHD medications (stimulants and non-stimulants) will be administered the ADHD-RS-5, CGI-S and ECG. Subjects who are currently taking ADHD medications (stimulants and non-stimulants) will be instructed to washout and come back on Visit 2 to obtain the ADHD-RS-5, CGI-S, ECG for eligibility (after an adequate washout of ADHD medications is confirmed). These subjects will be deemed eligible or not eligible at Visit 2.

Subjects may be rescreened 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.). The previous subject number must be recorded in the subject's study history.

7.1.1 VISIT 1 (SCREENING VISIT)

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

- Obtain Parental Permission and Written Informed Consent Assent
- Confirmation of ADHD Diagnosis utilizing ADHD-RS-5 (score of ≥ 28), and CGI-S (score of ≥4). This can be obtained at Visit 2 if washout from ADHD medications is needed
- Administer the MINI-KID
- Administer the C-SSRS (Baseline Version)
- Confirm Inclusion and Exclusion Criteria
- Collect Demographics
- Collect Medical History, including Prior and Concomitant Medications
- Perform Physical Examination
- Collect Vital Signs (included on eCRF Body Weight, Height, and BMI)
- Tablet Swallowing Test
- Perform 12-Lead ECG. This can be obtained at Visit 2 if washout from ADHD medications is needed

- Collect Blood and Urine Samples for Chemistry, Hematology, TSH, Serology, and Urinalysis
- Collect a urine sample for Drugs of Abuse
- Collect a urine sample for Methylphenidate
- Perform a Serum Screen for hCG in Females of Child-Bearing Potential
- Assess for Adverse Events
- Record Concomitant Medications
- Remind Subjects that they must washout of ADHD medications prior to the start of the Randomized Phase (Visit 2).
- Schedule next Day 0/ Study Visit 2

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 phone 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 if not on ADHD medications. Eligible subjects will be contacted by a member of the site staff and provided with instructions on discontinuing 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 there have been any changes in medical history since Screening; Assess for Adverse Events since Screening

7.1.3 VISIT 2

The following study-related procedures will be performed:

- Review and confirm that subject still meets Inclusion Criteria and No Exclusion Criteria

- Confirmation of ADHD Diagnosis utilizing ADHD-RS-5 (score of ≥ 28) and CGI-S (score of ≥4) if was not collected at Screening (Visit 1)
- Perform 12-Lead ECG, if it was not collected at Screening (Visit 1)
- Complete Prior Medication Questionnaire
- Perform Physical Examination
- Collect Vital Signs (included on eCRF Body Weight, Height, and BMI)
- Collect a urine sample for Drugs of Abuse
- Collect a urine sample for Methylphenidate for analysis by the central laboratory
- Perform a Urine hCG in Females of Child-Bearing Potential
- Administer the C-SSRS (Since Last Visit Version)
- Record Concomitant Medications
- Assess for Adverse Events
- Randomize Subject
- Dispense Study Drug (active or placebo, per IRT randomization)
- Distribute Dosing Diary
- Assign PK draw time for Day 1 (Visit 3) and Day 35 (Visit 8) (per IRT randomization)
- Remind Subject to take their dose prior to 8:00 am each day and schedule the Day 1 Visit

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. Efficacy assessments should be evaluated prior to any invasive study assessment.

7.1.4 VISIT 3

Drug Accountability and Compliance Assessments will begin at Visit 3 and continue at each Visit throughout the entire course of the study. Visit 3 will include the following study-related procedures:

- Collect Vital Signs (included on eCRF Body Weight, Height, and BMI)
- Record Concomitant Medications
- Assess for Adverse Events
- Drug Accountability and Compliance Assessment
- Collect Dose Time of IP
- Collect Blood Sample for Pharmacokinetic Assessment per PK Instructions
- Remind Subject to take their dose prior to 8:00 am each day
- Schedule or confirm upcoming study visits 4-8

7.1.5 VISIT 4 - VISIT 7

Visit 4-7 will include the following study-related procedures:

- Administer the ADHD-RS-5
- Administer the CGI-S
- Collect Vital Signs (included on eCRF Body Weight, Height, and BMI)
- Perform a Urine hCG in females of childbearing potential
- Administer the C-SSRS (Since Last Visit Version)
- Drug Accountability and Compliance Assessment
- Record Concomitant Medications
- Assess for Adverse Events
- Dispense Study Drug (must be at stable dose)
- Collect/Distribute Dosing Diary
- Remind Subject to Take Their Dose Prior to 8:00 am Each Day
- Schedule or confirm upcoming study visits 4-8. At Visit 7, confirm Visit 8 date and time according to the assigned time window for PK draw

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. Efficacy assessments should be evaluated prior to any invasive study assessment.

7.1.6 VISIT 8/ EARLY TERMINATION

Visit 8 will include the following study-related procedures:

- Administer the ADHD-RS-5
- Administer the CGI-S & CGI-I
- Collect Vital Signs (included on eCRF Body Weight, Height, and BMI)
- Perform Physical Examination
- Collect a urine sample for Drugs of Abuse
- Administer the C-SSRS (Since Last Visit Version)
- Perform 12-Lead ECG
- Collect Dose Time of IP Just Prior to Blood Draw
- Collect Blood and Urine Samples for Chemistry, Hematology, and Urinalysis
- Collect Blood Sample for Pharmacokinetic Assessment per PK instructions

- Perform a urine and serum screen for hCG in females of childbearing potential
- Drug Accountability and Compliance Assessment
- Collect/Review Dosing Diary
- Record Concomitant Medications
- Assess for Adverse Events
- Schedule or confirm upcoming study visit 9

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. Efficacy assessments should be evaluated prior to any invasive study assessment.

7.1.7 VISIT 9

Visit 9 is a safety follow-up phone call and subject will be washed out of drug. Visit 9 includes the following study-related procedures:

- Assess for Adverse Events
- Record Concomitant Medications

7.2 EARLY TERMINATION

If possible, Early Termination Visits should follow the Visit 8 procedures.

7.3 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from CTx-1301 does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine further or additional intervention with participant. Any new clinically relevant finding will be reported as an adverse event (AE) or SAE such as overdosage, etc.

7.4 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. Procedures conducted at an unscheduled visit must be recorded in the CRF.

7.5 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

8.1 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 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.

AEs are collected from the time of the informed consent is signed until the end of the study. 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 (Day 0) 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 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 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

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

- 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

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

A copy of the SAE form provided in the Investigator Site File should be completed within 24 hours of the investigator or study staff becoming aware of the event and provide to the following contact:

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 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 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.

O*ther SUSARs*: reporting to the Ethics Committee and FDA within 15 days of first becoming aware of the event.

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. A copy of the Pregnancy Form provided in the Investigator Site File should be completed within 24 hours of the investigator or study staff becoming aware of the pregnancy and provide to the following contact:

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 Screening (Visit 1), and Week 5 (Visit 8) to ensure the subject's good health and to ensure safety. 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) 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 Investigator, 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/lab 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 each 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 eCRF 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 SAMPLE SIZE CALCULATION

A pivotal Phase 3 study (2301) for Focalin XR shows a change-from-baseline mean difference b/w treatment and placebo of 10.4 with a pooled stdev=14.76, corresponding to an effect size of approximately 0.7 in CADS-T total score in the 6-12yr age. Similarities were identified in the CADS-T and the ADHD-RS-5 scales in that they both appear to be narrow band and focus on ADHD core symptoms, evaluate ADHD using 18 items in the DSM criteria, and evaluate functional impairment in terms of learning, behavior, and relationships (insert reference). Therefore, an effect size of 0.60 is assumed in this study for the comparison of mean change from baseline to week 5 in subjects receiving fixed doses of CTx-1301 and placebo. Approximately 77 subjects per treatment group (CTx-1301 18.75 mg: 25 mg: 37.5 mg: placebo=1:1:1:1) would provide 90% power at a 2-sided significance level of 0.017 based on a two-sample t test with effect size 0.60 after Bonferroni correction (nQuery Version 8.4.1.0), which results in a total sample size of 308. Assuming a drop-out rate of 20%, approximately 385 subjects will be enrolled.

9.4 ANALYSIS POPULATIONS

Intent-to-Treat (ITT) Population: Subjects who are randomized.

Safety (SAF) Population: Subjects who have received at least one dose of study drug.

Modified ITT (mITT) Population: subjects in the ITT population and have at least one post-baseline ADHD-RS-5 assessment.

Per Protocol (PP) Population: Subjects in the ITT population who have no major protocol deviations that interfere with the primary efficacy analysis. The PP Population will be determined in a blinded manner prior to database lock.

9.5 DATA ANALYSIS

9.5.1 SUBJECT DISPOSITION

Subject disposition will be summarized for randomized subjects. Subjects who complete the study and early withdraw from the study, including reason for early withdrawal will be summarized by treatment group.

9.5.2 DRUG EXPOSURE AND COMPLIANCE

Study drug exposure and drug compliance will be summarized descriptively in the safety population.

9.5.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized by age group (6-12 and 13-17) and overall, in the ITT and safety populations.

9.5.4 MEDICAL HISTORY

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

9.5.5 PSYCHIATRIC HISTORY

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

9.6 STATISTICAL CONSIDERATIONS

9.6.1 STATISTICAL APPROACH

Analysis Populations: Baseline analysis will be performed using the ITT and safety Populations. Efficacy analysis will be performed using the ITT, mITT, and PP populations. Safety analysis will be performed in the safety population.

Efficacy analysis: The primary efficacy analysis will be conducted in the ITT population, with supportive analyses conducted in the mITT and per protocol (PP) populations. Missing data will be imputed with multiple imputation. The CGI-S will be analyzed similarly using MMRM in the ITT population.

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

- Continuous data: n, mean, standard deviation, median, minimum, and maximum
- Categorical data: n/N and percent per arm (Placebo and each fixed dose CTx-1301)

Missing Data: The following applies to the primary endpoint and is applicable to analysis of efficacy data collected in the randomized double-blind portion of the study. A sensitivity

analysis using tipping point methods will be performed. Details of the sensitivity analysis will be included in the SAP.

9.6.2 PRIMARY EFFICACY ENDPOINT ANALYSIS

The primary efficacy endpoint is defined as the change in the ADHD-RS-5 Total Score from baseline to week 5.

The estimand for the primary efficacy endpoint of this study is defined here in accordance with the ICH E9 Addendum:

1. Population: The population targeted for the scientific questions is defined via the inclusion and exclusion criteria in children aged 6 to 17 years diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) confirmed by an ADHD-Rating Scale (RS)-5 score of at least 28 and Clinical Global Impressions Scale (CGI-S) score of 4 or higher at baseline.
2. Variable (or endpoint): Change from baseline to week 5 of the treatment period in ADHD-RS-5 total score. Each of the 18 items on the scale are rated from 0 (rarely) to 3 (very often). The sum of the scores for the 18 items provides the total score ranging from 0 to 54.
3. Intercurrent Events: A treatment policy strategy has been adopted for handling all known or unknown intercurrent events in this study. To this end, the ITT principle will serve as the analytical basis for interpreting the estimand. See SAP for more details on analysis visit mapping for early termination subjects.
4. Population level summary: The change of ADHD-RS-5 total score from baseline to week 5 will be analyzed using a mixed model for repeated measures (MMRM). MMRM assumes the data are missing at random (MAR). Missing data will be accounted for by the model.

The observed and change from Baseline ADHD-RS-5 will be summarized at each applicable visit using the number of subjects, mean, standard deviation, median, minimum, and maximum values. Results will be presented by age group (6-12, 13-17) and overall.

The null hypotheses for the primary efficacy endpoint of the equality of CTx-1301 and placebo is:

- H01,1: mean change in ADHD-RS-5 total score between baseline and Visit 8week 5 between the 18.75 mg CTx-1301 and placebo groups are equal
- H01,2: mean change in ADHD-RS-5 total score between baseline and week 5Visit 8 between the 25 mg CTx-1301 and placebo groups are equal
- H01,3: mean change in ADHD-RS-5 total score between baseline and week 5Visit 8 between the 37.5 mg CTx-1301 and placebo groups are equal

The alternative hypothesis for the primary efficacy endpoint of the equality of CTx-1301 and placebo is:

- H_a: mean change in ADHD-RS-5 total score between baseline and week 5 between any CTx-1301 fixed dose (18.75, 25, 37.5) and placebo groups are not equal

The study will be considered successful if any one (or more) of the above null hypotheses are rejected.

The estimate of the difference between CTx-1301 (active) and placebo will be analyzed using a mixed-effects model for repeated measures (MMRM) with change from baseline as the dependent variable, visit, treatment group, age group, and the interaction of visit and treatment group as fixed effects with baseline ADHD-RS-5 as a covariate. To protect the study-wide Type I error rate at the 2-sided 0.05 level for testing across multiple dosage groups on the primary endpoint, Bonferroni correction is applied so that the hypothesis in each dose group is tested at alpha = 0.017 level. More details in the primary efficacy analysis will be described in the Statistical Analysis Plan (SAP).

9.6.3 KEY SECONDARY EFFICACY ENDPOINT ANALYSIS

The key secondary endpoint is defined as the change in the CGI-S score from baseline to week 5. CGI-S will be analyzed using the same MMRM model, as described above. The baseline CGI-S score will be used as the covariate.

The null hypothesis for the key secondary efficacy endpoint of the equality of CTx-1301 and placebo is:

H02: mean change in CGI-S score between baseline and week 5 in the treatment groups are equal.

The key secondary endpoint (CGI-S) in each dose group will be analyzed following the fixed-sequential (hierarchical) testing procedure. If the hypothesis is significant for the primary endpoint at the 2-sided 0.017 significance level, the key secondary endpoint will be analyzed.

9.7 PK ANALYSIS

Pharmacokinetic parameters for individual subjects will be evaluated at Day 1 (Visit 3) for single dose pk and Week 5 (Visit 8) steady state. The pharmacokinetic samples collected will be used to model and simulate the following pharmacokinetic parameters using population PK: Maximum Concentration (C_{max}), Time of Maximum Concentration (T_{max}), terminal elimination constant (K), lag time (T_{lag}), Half Life ($T_{1/2}$), Area Under the Curve from time 0 to 28 hrs (AUC_{last}), Area Under the Curve from time 0 to infinity ($AUC_{0-¥}$), and partial areas AUC_{0-3}, AUC_{3-6}, AUC_{3-7}, AUC_{6-9}, AUC_{7-12}, AUC_{9-12}, and AUC_{12-16}. Additional measures may be evaluated if deemed necessary. PK parameters will be evaluated by study visit, time post-dose, and by age group.

Additional details of pharmacokinetic analysis will be included in a separate PK analysis plan.

9.8 SAFETY

The safety data will be analyzed on the safety set. Safety endpoints include the occurrence of TEAEs, vital signs, blood labs, physical exams, BMI, and weight, C-SSRS, and ECG 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, physical exams, and BMI will be summarized by treatment and visit using the appropriate descriptive statistics.

9.9 OTHER SECONDARY ENDPOINT ANALYSIS

CGI-I collected at Visit 8 or early termination will be summarized by treatment group and age group.

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

The Investigator, or designated study staff, must obtain written (signed and dated) IRB-approved parental permission and informed consent from the parent/legal guardian, and/or caregiver (if applicable) 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 and prior to conducting any study specific procedures (i.e., any procedures described in the protocol). There must also be written (signed and dated) assent indication that the subject is aware of the investigational nature of the study, and the required procedures and restrictions, prior to the performance of any study-related procedures. The process of obtaining informed consent and assent should be documented in the subject source documents.

The Investigator, or designated study staff, must also explain to the subjects, parent/legal guardian, and/or caregiver (if applicable) 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 and assent must be obtained prior to any study procedures being conducted. The Investigator, or designated study staff, should sign and date the consent and assent form to confirm that the consent process was completed correctly and the subject, parent/legal guardian, and/or caregiver (if applicable) has fully understood the objectives of the study as well as the risks.

The subject, legal guardian, and/or caregiver (if applicable) will be provided with a copy of their signed and dated consent and assent 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.

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 and assent form and active subjects will be re-consented.

10.3 FDA

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

10.4 INSTITUTIONAL REVIEW BOARD (IRB)

This protocol (and any modifications) as well as appropriate consent procedures, will be reviewed and approved by an Institutional Review Board (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 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 IRB responsible for the study.

The outcome of the study (e.g., completed) will be reported to the 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 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 CRF). 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 approvals for the study protocol and amendments,
- Source documents and laboratory records,
- CRF 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 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 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).

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

The study monitor(s) will review 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 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.

Major/substantial protocol modifications/amendments must be reviewed and approved by the IRB. Approvals from the 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 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, parent/legal guardian, and/or caregiver (if applicable) 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, parties are bound to keep this information confidential.

The investigator will guarantee that persons involved will respect the confidentiality of any information concerning the trial subjects. 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 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 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).

17 DISCLOSURE OF INFORMATION

Information provided to the Investigator by Cingulate Therapeutics 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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