STATISTICAL ANALYSIS PLAN

STUDY TITLE:

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

PROTOCOL NUMBER:

CTX-1301-022

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ACKNOWLEDGEMENT AND SIGNATURE SHEET

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VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	10 Feb 2023	N/A	Initial version
2.0	22 Jun 2023	Updated language around efficacy visit windowing/assignment	Efficacy analyses

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS 7
2. PURPOSE OF THE ANALYSES 9
3. PROTOCOL SUMMARY 10
3.1. Study Objectives 10
3.2. Overall Study Design and Plan 10
3.3. Study Population 11
3.4. Treatment Regimens 11
3.5. Sample Size Determination 12
4. GENERAL ANALYSIS AND REPORTING CONVENTIONS 13
5. ANALYSIS SETS 14
6. STUDY SUBJECTS 15
6.1. Disposition of Subjects 15
6.2. Demographic and Other Baseline Characteristics 15
6.3. Prior and Concomitant Medications 15
6.4. Medical History 16
6.5. Psychiatric History 16
7. STUDY OPERATIONS 17
7.1. Protocol Deviations 17
7.2. Randomization 17
7.3. Measures of Treatment Compliance 17
8. ENDPOINT EVALUATION 18
8.1. Overview of Efficacy Analysis Methods 18
8.1.1. Multicenter Studies 18
8.1.2. Assessment Time Windows 18
8.1.3. Timing of Analyses 19
8.1.4. Multiple Comparisons/Multiplicity 19
8.2. Primary Endpoint 19
8.3. Secondary Endpoints 20
8.3.1. Change from baseline (pre-dose) in PERMP-C scores measured at each Visit 8 post-baseline timepoint 20

8.3.2. Change in CGI-S from pre-dose at Visit 2 to post-dose at Visit 8 20
8.4. Other Endpoints 21
8.4.1. Exploratory Efficacy Endpoints 21
8.4.2. AISRS 21
8.4.3. CGI-S 21
8.4.4. CGI-I 21
8.5. Examination of Subgroups 21
9. SAFETY EVALUATION 22
9.1. Overview of Safety Analysis Methods 22
9.2. Extent of Exposure 22
9.3. Adverse Events 22
9.3.1. Summary Tabulations 22
9.3.2. System Organ Class and Preferred Term Tabulations 23
9.3.3. Imputation Rules for Missing AE Start/End Dates 23
9.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events 24
9.5. Clinical Laboratory Evaluation 24
9.6. Vital Signs, Physical Findings, and Other Observations Related to Safety 24
9.6.1. Vital Signs 24
9.6.2. Physical Examinations 24
9.6.3. ECGs 25
9.6.4. C-SSRS 25
10. PHARMACOKINETIC EVALUATION 26
11. OTHER ANALYSES 27
12. INTERIM ANALYSES AND DATA MONITORING 28
13. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL 29
14. REFERENCES 30
15. APPENDIX 31
15.1. Schedule of Events 31

List of Tables

Table 1: List of Abbreviations 7
Table 2: Study Visit and Time Point Windows 18

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ADHD	Attention-deficit/hyperactivity disorder
AISRS	Adult ADHD Investigator Symptom Rating Scale
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBS	double blind treatment phase safety
d-MPH	dexmethylphenidate
DOS	dose optimization phase safety
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECGs	electrocardiograms
eCRF	electronic case report form
HR	heart rate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OS	overall safety
PERMP	Permanent Product Measure of Performance
PERMP-C	PERMP number of problems correct
PT	preferred term
QTcB	QTc with Bazett correction
QTcF	QTc with Fredericia correction
SAEs	serious adverse events
SAP	statistical analysis plan

SD	standard deviation
SOC	system organ class
TEAEs	treatment-emergent adverse events
WHO	World Health Organization

2. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives for protocol CTx-1301-022. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Deviations from the final approved plan will be noted in the clinical study report (CSR).

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, listings, and figures.

3. PROTOCOL SUMMARY

3.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of CTx-1301 compared to placebo in treating adults with Attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting

The secondary objectives of this study are:

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

The exploratory objective of this study is:

- To evaluate quality and satisfaction of prior medication to investigational product

3.2. Overall Study Design and Plan

This is a single-center, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy and safety laboratory classroom study with CTx-1301 in adults with ADHD confirmed by an Adult ADHD Investigator Symptom Rating Scale (AISRS) score of at least 24 and Clinical Global Impression Severity (CGI-S) score of at least 4 (moderately ill) at Screening. The study will be comprised of a screening period, a dose-optimization phase, a double-blind randomized phase, and a safety follow-up phase.

The study will be comprised of 4 periods:

- **Screening Period (Day -45 to Day -1)**: Subjects will undergo a Screening Visit up to 45 days prior to entering the 5-week, dose-optimization phase. Only subjects who meet all inclusion and no exclusion criteria at Screening may be considered for the dose-optimization phase. A reminder telephone call will be completed 5 days prior to Day 0 of the optimization period to ensure washout of current prohibited medications, to confirm inclusion/exclusion criteria, and to confirm date of next visit.
- **Dose Optimization Phase (Day 0 to Day 35 ± 3 days)**: During the 5-week, dose-optimization phase, subjects will have weekly visits and will be titrated to doses ranging between 25.0 – 50.0 mg of CTx-1301. Subjects' starting dose will be 25.0 mg. The optimal dose will be determined with weekly visits by evaluating tolerability, safety, best individual subject-dose response using the AISRS, CGI-S, and the opinion of the Investigator. Each subject is expected to be in the dose-optimization phase for 5 weeks, thus allowing one extra week if subjects require adjustment to achieve their "optimized dose", including a lower or higher dose during the optimization phase. Each subject is required to be on their optimal dose a minimum of 2 sequential weeks prior to the 7-day, double-blind, randomized, efficacy period.

  Visit 7 is the last day of the dose optimization period. At Visit 7, the investigational medication must be administered by the site. Breakfast will be provided at approximately

60 minutes post dose (+ 15 minutes), following the 60-minute post-dose Permanent Product Measure of Performance (PERMP) assessment. Lunch will be provided at approximately 12:00 PM (± 30 minutes).

- **Double-Blind, Placebo-Controlled, Randomized Efficacy Phase (Day 35 to Day 42 ± 3 days)**: Prior to randomization of the double-blind treatment at Visit 7, subjects are confirmed to be eligible to continue onto the double-blind, randomized phase. Eligible subjects will be randomized to either their optimal CTx-1301 dose, or placebo. The randomized dose of CTx-1301 will be the final optimized dose as determined during the dose-optimization phase (active), or placebo. All subjects will receive their assigned treatment for 7 days (± 3 days). All efficacy assessments will be performed after the last dose of the randomized, efficacy phase at Visit 8.

  At Visit 8, the investigational medication must be administered by the site. Breakfast will be provided at approximately 60 minutes post dose (+ 15 minutes), following the 60-minute post-dose PERMP assessment. Lunch will be provided at approximately 12:00 PM (± 30 minutes) and dinner will be provided at approximately 6:00 PM (± 30 minutes).

- **Safety Follow-Up Visit (Day 49 ± 3 days)**: Subjects will have an in-clinic visit as a safety follow up; the safety follow up will be completed within 7 days (± 3 days) after the full ALC visit (Visit 8).

3.3. Study Population

This study will investigate the safety and efficacy of CTx-301 in 18- to 55-year-old subjects. Assuming a dropout rate of 20%, approximately 25 subjects will be enrolled in the dose optimization phase of the study to achieve completion of approximately 20 subjects in the randomization phase. The study will take place at 1 site in the United States.

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

Dropouts will not be replaced.

3.4. Treatment Regimens

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

- 25.0 mg
- 37.5 mg
- 50.0 mg

All doses are the same shape and size, regardless of strength.

The comparator product is a matching placebo tablet. Placebo will be used if subjects are randomized to the placebo arm during the 7-day, double-blind, randomized, treatment phase.

All subjects will be titrated to their optimal dose during the dose-optimization phase. Subjects starting dose will be 25.0 mg. The optimal dose will be determined with weekly visits by evaluating tolerability, safety, best individual subject dose-response using AISRS (since the prior visit), CGI-S, and the opinion of the Investigator.

3.5. Sample Size Determination

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

H_0: The change from Visit 8 baseline in average PERMP scores across Visit 8 post-dose measurements does not differ between CTx-1301 and placebo

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

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

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

4. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following general analysis and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). If a count is 0, no percentage will be shown. To ensure completeness, summaries for categorical variables will include all categories, even if no subjects had a response in a particular category. Denominators will include subjects with non-missing data, unless otherwise specified. The number of subjects with missing data for categorical variables will be summarized without a percentage.
- Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of subjects. The mean, median, and confidence intervals (CI) will be rounded and reported to 1 more level of precision than the original observations, and the SD will be rounded and reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.
- Following SAS default rules, the median will be reported as the rounded average of the two middle numbers if the dataset contains even numbers.
- P-values, if any are provided, will be rounded and reported to 3 decimal places if greater than 0.001. If the rounded p-value is less than 0.001, '<0.001' will be reported. If the rounded p-value is >0.999, '>0.999' will be reported.
- Unless otherwise specified, the baseline value for all measures is the last non-missing value prior to the first dose, obtained on or before the date of the first dose of study drug. For measurements that occur on the date of the first dose of study drug with time collected, the measurement will be considered the baseline value if the measurement time is prior to the time of the first dose.
- No preliminary rounding will be performed; rounding will only occur after analysis. To round, consider digit to right of last significant digit: if < 5 then round down, if ≥ 5 then round up.
- All listings will be sorted in order of subject, parameter (when applicable), and time of assessment (e.g., visit, time, and/or event).
- Dates in listings will be displayed as yyyy-mm-dd (e.g., 2021-10-14).
- Age (in years) will be calculated as [(date of informed consent – date of birth)] /365.25 and will be reported as the integer part of the derived age, with no rounding, in the analysis datasets, tables, and listings.
- All analyses will be performed using the SAS System version 9.4.

5. ANALYSIS SETS

The study analysis populations will consist of:

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

- **Dose Optimization Phase Safety (DOS) Population:** All subjects who received at least one dose of study medication during the dose optimization phase.

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

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

6. STUDY SUBJECTS

6.1. Disposition of Subjects

Patient accountability will be summarized based on all patients screened into the study, and for each treatment group and overall. The following patient accountability information will be presented:

- The overall number of subjects who were screened, rescreened, enrolled, and randomized
- The number and percentage of enrolled subjects who completed each study phase, and who prematurely discontinued from the study during each study phase
- The number and percentage of enrolled subjects in each analysis set
- The number and percentage of enrolled subjects who discontinued prematurely by reason for premature discontinuation, by study overall and by study phase

Subject disposition will be listed for all enrolled subjects in a listing which shows treatment assignment, patient number, sex, age, race, reason for discontinuation, and any specific comments related to discontinuation.

Screen failures and their reason for failure will be listed.

6.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics including age (continuous), sex, race, ethnicity, ADHD type, response using stimulant medications, height, weight, body mass index (BMI), and BMI z-score will be summarized by treatment group and overall, for the OS and mITT populations.

Demographic and baseline characteristics data will be listed for subjects in the OS population.

6.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary (WHO Drug), Global version (2022-SEP) to identify the drug class and preferred drug name.

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

The number and percentage of subjects using prior medications, and separately concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) level 3 term, and preferred drug name for all subjects in the OS population. A subject will be counted at most once within each ATC level 3 term, and preferred drug name combination. All percentages will use

the number of subjects in the population Set as the denominator. The tabular summaries will be sorted by descending overall frequency by ATC level 3 term, and preferred drug name.

Prior and concomitant medication data, as well as subjects' lifetime ADHD medication history will be presented in data listings for subjects in the OS population.

6.4. Medical History

Medical history findings will be coded using MedDRA Version 25.1 and will be summarized descriptively by treatment group on the OS population.

Medical history will be presented in data listings for subjects in the OS population.

6.5. Psychiatric History

Psychiatric history will be summarized by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The count and percentage of subjects under each DSM-5 code will be summarized using the OS population.

Psychiatric history will be presented in data listings for subjects in the OS population.

7. STUDY OPERATIONS

7.1. Protocol Deviations

Protocol deviations will be presented for the OS population. The number and percentage of subjects with major and minor deviations will be presented for each study phase for each treatment group and overall.

Protocol deviations will be identified and displayed in data listings by study phase, treatment group, subject, study day and (where applicable) date of deviation.

7.2. Randomization

The treatment given to individual subjects during the double-blind, randomized, efficacy phase of the study is determined by a randomization schedule; the randomization schedule will assign eligible subjects to 1 of 2 treatment groups and be in an allocation ratio of 1:1 (CTx-1301: placebo). The actual treatment assigned to each subject is executed by an IRT system utilizing the randomization schedule. All investigational products (CTx-1301and placebo) will appear identical to ensure blinding. Assuming a drop-out rate of approximately 20% from the start of dose-optimization to the randomization phase, approximately 25 subjects will be required to enter the dose-optimization period of the study.

Randomization date and treatment assignment will be listed for randomized subjects.

7.3. Measures of Treatment Compliance

Compliance will be assessed by counting tablets and dividing the actual number of doses taken (per tablet count) by the number of doses the subject should have taken within a visit period and multiplying by 100. Subjects who miss more than 25% of scheduled doses or take more than 125% of scheduled doses will be considered non-compliant. The number and percentage of compliant subjects by study phase will be summarized by treatment group using the appropriate safety set.

8. ENDPOINT EVALUATION

8.1. Overview of Efficacy Analysis Methods

8.1.1. Multicenter Studies

This is a single-center study.

8.1.2. Assessment Time Windows

The nominal visit will be used for all efficacy analyses. Protocol deviations will be evaluated to determine whether nominal visit data should be excluded. Unscheduled and early termination visits will be listed but will not be displayed separately in the summaries.

For unscheduled and early termination visits, analysis windows listed in Table 2 will be used in efficacy analyses to slot actual efficacy assessment dates into planned assessment schedule. Early termination visit and unscheduled visit efficacy data will be included in the analyses if no scheduled visit data is available for the nominal case report form (CRF) visit. If more than one unscheduled assessment (early termination or unscheduled) is performed within an analysis window, the assessment performed closest to the target day or time point will be used.

Table 2: Study Visit and Time Point Windows

Study Phase **Visit** **Time Point**	**Visit Number**	**Study Day**	**Analysis Window[a]**
Screening			
Screening	1	-30 to -1	N/A
Washout Call	1.5	-5	N/A
Dose-Optimization			
Visit 2	2	1	1
Visit 3	3	8	2-11
Visit 4	4	15	12-18
Visit 5	5	22	19-25
Visit 6	6	29	26-32
Visit 7 (Practice ALC)	7	36	33-39
Pre-dose	7	36	N/A
0.5 hours post-dose			1-45 mins
1 hour post-dose			≥45-120 mins
3 hours post-dose			≥2-4.5 hours
6 hours post-dose			≥4.5 hours
Double-blind, Placebo-Controlled, Randomized Efficacy			
Visit 8	8	43	40-46
Pre-dose	8	43	N/A
0.5 hours post-dose			1-45 mins

1 hour post-dose			≥45-120 mins
3 hours post-dose			≥2-4.5 hours
6 hours post-dose			≥4.5-7.5 hours
9 hours post-dose			≥7.5-10.5 hours
12 hours post-dose			≥10.5-12.5 hours
13 hours post-dose			≥12.5-13.5 hours
14 hours post-dose			≥13.5-14.5 hours
15 hours post-dose			≥14.5-15.5 hours
16 hours post-dose			≥15.5 hours
Safety Follow-up			
Visit 9	9	50	≥ 47
[a]Analysis windows for the Screening visits are not defined and visit assignments are based on the nominal CRF visits. Analysis windows for visits on or after enrollment are defined using the midpoints between each scheduled visit and will be used to map early termination or unscheduled visit data to scheduled visits. Analysis windows for pre-dose timepoints are not defined and the last measurement prior to the morning dosing will be used.			

8.1.3. Timing of Analyses

Analyses of safety and efficacy are planned after all subjects complete the final study visit or terminate early from the study and once the study is unblinded.

8.1.4. Multiple Comparisons/Multiplicity

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

8.2. Primary Endpoint

Variable: Change from baseline (pre-dose) in PERMP number of problems correct (PERMP-C) scores over the day during Visit 8.

Population: The analysis population will be the mITT population which is comprised of adults aged 18-55 with ADHD as defined by the protocol inclusion/exclusion criteria.

Intercurrent events: Subjects who discontinue the study early might be outcome dependent. As a sensitivity analysis, missing timepoints at Visit 8 will be imputed using subjects' baseline PERMP-C scores (i.e., impute as no change from baseline).

Population-level summary: Comparison between treatment groups of the average change from baseline in PERMP-C scores over the day during Visit 8.

Computation: For each subject that enters the double-blind treatment phase, the change in PERMP-C score from baseline (pre-dose) will be calculated at each Visit 8 post-baseline timepoint as (score – baseline score). The mean of the changes from baseline within each subject will be used in the primary efficacy analysis.

Analysis: The change from baseline between CTx-1301 (active) and placebo for the PERMP-C score will be analyzed by using an Analysis of Covariance (ANCOVA) model with treatment group as a fixed effect and baseline PERMP-C score as a covariate for the mITT population. The treatment comparison will be conducted as a two-sided test at the 5% level of significance. Standard errors and 95% confidence intervals will be calculated. Treatment difference and effect size will be presented.

8.3. Secondary Endpoints

The Key Secondary Efficacy Endpoints are:

- Change from baseline (pre-dose) of the PERMP-C scores measured at each Visit 8 post-baseline timepoint
- Change in Clinical Global Impression-Severity (CGI-S) from pre-dose at Visit 2 to post-dose at Visit 8

8.3.1. Change from baseline (pre-dose) in PERMP-C scores measured at each Visit 8 post-baseline timepoint

Variable: Change from baseline (pre-dose) in PERMP-C scores measured at each post-baseline timepoint during Visit 8.

Population: The analysis population will be the mITT population which is comprised of adults aged 18-55 with ADHD as defined by the protocol inclusion/exclusion criteria.

Intercurrent events: Subjects who discontinue the study early might be outcome dependent. As a sensitivity analysis, missing timepoints at Visit 8 will be imputed using subjects' baseline PERMP-C scores (i.e., impute as no change from baseline).

Population-level summary: Comparison between treatment groups of the change from baseline in PERMP-C scores at each post-baseline timepoint during Visit 8.

Computation: The change in PERMP-C score from baseline (pre-dose) will be calculated at each Visit 8 post-baseline timepoint as (score – baseline score).

Analysis: The changes in PERMP-C scores will be analyzed similarly to the primary endpoint and will be reported by timepoint.

8.3.2. Change in CGI-S from pre-dose at Visit 2 to post-dose at Visit 8

Variable: Change in CGI-S from pre-dose at Visit 2 to post-dose at Visit 8 in CGI-S.

Population: The analysis population will be the mITT population which is comprised of adults aged 18-55 with ADHD as defined by the protocol inclusion/exclusion criteria.

Intercurrent events: Subjects who discontinue the study early might be outcome dependent. As a sensitivity analysis, missing data at Visit 8 will be imputed using subjects' pre-dose at Visit 2 CGI-S scores (i.e., impute as no change).

Population-level summary: Comparison between treatment groups of the change in CGI-S from pre-dose at Visit 2 scores to post-dose at Visit 8.

Computation: CGI-S scores range from 1-7. The change in CGI-S score from baseline (pre-dose at Visit 2) to post-dose at Visit 8 will be calculated as (post-dose at Visit 8 score – pre-dose at Visit 2 score).

Analysis: The change in CGI-S score will be analyzed similarly to the primary endpoint, with treatment group as a fixed effect and pre-dose at Visit 2 CGI-S score as a covariate for the mITT population.

8.4. Other Endpoints

8.4.1. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will evaluate the efficacy of CTx-1301 during the dose optimization phase by assessing the following:

- Evaluate overall treatment experience of subjects who were on stable ADHD stimulant medications within the 30 days prior to Screening compared to CTx-1301 at the end of dose optimization phase by utilizing the provided entrance and exit questionnaires.

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

8.4.2. AISRS

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

AISRS total score, inattentive subscale score, and hyperactive impulsive subscale score, will be summarized by visit, including change from baseline, and percent change from baseline, and presented for the dose-optimization and double-blind phases by treatment group for the mITT population.

8.4.3. CGI-S

CGI-S score and change from baseline (as categorical change of the difference in score) will be summarized by visit and presented for the dose-optimization phase for the mITT population.

8.4.4. CGI-I

Clinical Global Impression – Improvement (CGI-I) score will be summarized categorically at Visit 7 by treatment group for the mITT population.

8.5. Examination of Subgroups

No subgroup analysis will be performed.

9. SAFETY EVALUATION

Safety will be analyzed for each of the safety populations. Safety endpoints include the occurrence of Treatment-Emergent Adverse Events (TEAEs) post dose.

All adverse events (AEs) will be listed for each subject and summarized by the body system and preferred term assigned to the event using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Any serious adverse events will be listed separately.

AEs, vital signs, height and weight, appetite, sleep, physical examinations, electrocardiograms (ECGs), clinical laboratory measurements, and Columbia-Suicide Severity Rating Scale (C-SSRS) scores will be evaluated for safety.

9.1. Overview of Safety Analysis Methods

9.2. Extent of Exposure

The length of exposure (in days) of study drug will be calculated based on the dates of first and last dosing of study drug (last dosing date - first dosing date + 1), separately for the dose-optimization phase, double-blind phase, and overall. Length of exposure will be summarized by optimized dose (25 mg, 37.5 mg, 50 mg) and treatment group on the safety populations as continuous values.

9.3. Adverse Events

All AEs and serious adverse events (SAEs) will be recorded from the time of informed consent until the end of the study. An AE is considered treatment emergent if it started during or after administration of the first dose of study drug. In addition, medical history events that worsen in severity after the start of dosing will be considered TEAEs. AEs with partial start dates will be imputed as outlined in Section 9.3.3 and assigned to the associated treatment period. All AEs will be coded using MedDRA Version 25.1.

9.3.1. Summary Tabulations

The frequency of subjects reporting TEAEs will be summarized within each system organ class. An overview of the frequency and the number and percentage of subjects with at least one of the following AEs will be presented for the dose-optimization and double-blind phases by treatment group and overall:

- TEAEs
- TEAEs related to study drug
- Severe TEAEs
- SAEs
- SAEs related to study drug

- AEs leading to premature withdrawal of study drug
- AEs leading to death

9.3.2. System Organ Class and Preferred Term Tabulations

The frequency of subjects reporting TEAEs will be summarized within each system organ class (SOC) and preferred term (PT), for the dose-optimization phase and double-blind phase by treatment group. The SOC terms and PTs will be presented in decreasing order of the total number of subjects (frequency) who experienced each AE. SOC terms and PTs with the same frequency will be presented alphabetically.

Each AE will be summarized by treatment period in which the AE started. If an AE started in the dose-optimization phase and continued into the double-blind phase, the AE will be counted only in the dose-optimization phase.

If a single subject experienced the same AE more than once within a treatment period, the subject will be counted once per SOC and PT for that AE. For subjects that experienced AEs with multiple severities, the AE with the worst severity will be counted.

Adverse events with unassigned/unknown severity will be categorized as severe. Events with unassigned/unknown relationship to study medication will be considered related to study drug.

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

- TEAEs
- TEAEs related to study drug
- TEAEs by severity

Listings for all reported adverse events will be presented by study phase for the OS population.

9.3.3. Imputation Rules for Missing AE Start/End Dates

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

- If only the year is known, the date will be set to 01 January of that year. If the year is the same as the year of the first dose of study drug, the date will be set to the date of the first dose of study drug.
- If the year and month are known, the date will be set to first day of the month. If the year and month are the same as the year and month of the first dose of study drug, the date will be set to the date of the first dose of study drug.
- If the start date is completely missing, it will be set to the date of the first dose of study drug.
- If the above rules result in a start date that is after the end date, the start date will be set to the end date.

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

9.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

The frequency of subjects reporting the following AEs will be presented by SOC and PT according to the methods in Section 9.3.2:

- Treatment-emergent SAEs
- TEAEs leading to premature withdrawal of study drug
- Fatal TEAEs

Listings for SAEs, TEAEs leading to premature withdrawal of study drug, and fatal AEs will be presented for the OS population.

9.5. Clinical Laboratory Evaluation

Chemistry, hematology, serology, and urinalysis laboratory tests will be performed at Screening, Baseline, Visit 8, and the Safety Follow-up Visit. All laboratory values will be presented in data listings for the OS population.

For continuous laboratory parameters, descriptive statistics will be presented for the value at each assessment time and for the change from baseline for Visit 2 to the Safety Follow-up Visit. For categorical parameters, absolute and relative frequencies will be tabulated at each visit.

9.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.6.1. Vital Signs

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

Height, weight, BMI, and BMI z-score, calculated using the CDC growth chart, will be summarized descriptively for Visit 1, Visit 2, and Visit 9 by treatment group, including change from baseline.

Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature will be summarized descriptively for each visit in the dose-optimization phase and separately in the double-blind phase by treatment group, including change from baseline.

Vital signs will be listed for the OS population.

9.6.2. Physical Examinations

A full physical examination will be performed at Visit 1, Visit 2, and Visit 9.

Abnormal physical exam results will appear in medical history and/or adverse events displays and will not be displayed separately.

9.6.3. ECGs

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. Results and changes from baseline will be summarized descriptively by visit, presented by treatment group. ECG interpretations, which include clinical significance, will also be summarized by visit, presented by treatment group.

ECG results will be listed for the OS population.

9.6.4. C-SSRS

The C-SSRS is a brief investigator-administered questionnaire that provides for the identification, quantification, and standardized assessment of the occurrences and severity of suicidal ideation and behavior. Subjects will be assessed at Screening using the Screening C-SSRS. For all subsequent testing (Visits 2 through 9 and the early termination visit), the Since Last Visit assessment will be utilized.

The frequency and percentage of suicidality using the C-SSRS will be summarized for each visit separately for the dose-optimization and double-blind phases by treatment group for each of the following outcomes:

- At least one occurrence of suicidal ideation or behavior.
- Any type of suicidal behavior.
- Any type of suicidal ideation.

10. PHARMACOKINETIC EVALUATION

No pharmacokinetic sampling is planned for this study.

11. OTHER ANALYSES

Any additional analyses performed after finalization of the SAP will be considered exploratory and will be identified as such in the CSR.

12. INTERIM ANALYSES AND DATA MONITORING

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

13. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

No changes are planned as of the date of the SAP.

14. REFERENCES

Not applicable.

15. APPENDIX

15.1. Schedule of Events

Procedure / Assessments	Screening/ Washout		Dose Optimization Phase (± 3 days)					Practice ALC (± 3 days)	Double-Blind Treatment Phase Full ALC (± 3 days)	Safety Follow-up Visit (± 3 days)
Study Day	-45 to -1	-5	0	7	14	21	28	35	42	49
Visit Number	1	Phone call	2	3	4	5	6	7[j]	8	9
Informed Consent	✔									
ADHD Diagnosis and Confirmation	✔		✔[a]							
PERMP Pre-Test			✔							
Inclusion & Exclusion Criteria	✔	✔	✔							
Demographics	✔									
Medical History	✔									
Physical Examination	✔		✔							✔
Body Weight, Height, BMI[b]	✔		✔							✔
12-Lead ECG	✔[c]		✔						✔	✔[c]
Vital Signs	✔		✔	✔	✔	✔	✔	✔	✔	✔
Chemistry, Hematology, Serology, Urinalysis	✔		✔						✔	✔
Serum hCG[g]	✔									✔
Urine hCG[g,h]			✔	✔	✔	✔	✔	✔	✔	
TSH	✔									
Breath Alcohol Test	✔		✔					✔	✔	
Urine Screen for Drugs of Abuse	✔		✔					✔	✔	
Urine MPH Screen	✔		✔							
C-SSRS[k] Baseline/Screening	✔									
C-SSRS[k] (Since Last Visit)			✔	✔	✔	✔	✔	✔	✔	✔
MINI	✔									
AISRS	✔		✔[f]	✔	✔	✔	✔	✔[f]	✔	
PERMP assessments				✔	✔	✔	✔	✔	✔	
CGI-S	✔		✔[f]	✔	✔	✔	✔		✔	
CGI-I								✔[f]		
AE Assessment[d]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Dose Optimization			✔	✔	✔	✔	✔			
Randomization[e]								✔[e]		
Double-Blind Study Drug Administration								✔	✔	
Drug Accountability & Compliance Assessment				✔	✔	✔	✔	✔	✔	
Concomitant Medications	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Entrance/Exit Questionnaire	✔							✔		
Study Completion/Medical Sign-Off										✔

a. If subject is on medication at Screening, investigator must confirm ADHD criteria after washout of medications at baseline (Visit 2) prior to dose titration.
b. Height and weight will be measured without shoes and with light clothing using a calibrated stadiometer and scale.
c. ECG assessed at Visit 1 and Visit 9 should be off medication per washout requirements.
d. AEs will be assessed throughout the study; AEs will be collected from time the informed consent is signed until end of the study. Any AEs occurring between visits should be attributed to the next study visit (or unscheduled visit), but the dates of the AE must be recorded as occurred. AEs occurring during the washout may be reported via phone or at the following visit.
e. Randomization will occur at the end of Visit 7.
f. CGI-I, AISRS, and safety to be evaluated for eligibility prior to randomization at Visit 7.
g. Females of child-bearing potential.
h. A positive urine hCG test will be confirmed with a serum hCG. A positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study.
i. Early Termination Visit should follow the Visit 9/Day 49 visit study assessment schedule.
j. At Visit 7, the Investigator will evaluate the eligibility criteria based on the efficacy and safety observed over the 5-week dose-optimization period in the Dose Optimization Phase, for continuation into the subsequent double-blind, randomized treatment phase. If subject meets all eligibility criteria, each subject will complete the practice ALC session with 4 PERMP assessments designed to mirror the pre-dose to 16-hour post-dose session of the full-length laboratory classroom day at Visit 8.
k. Columbia Suicide Severity Rating Scale (C-SSRS): The "Baseline" version will be assessed at Screening and "Since Last Visit" at Visits 2-9 and at Early Termination. Subjects who have, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study.

PROPRIETARY — [redacted]