Statistical Analysis Plan: CTx-1301-001

A randomized, single-dose, four-sequence, four-period, in-clinic crossover study in adult ADHD subjects to establish safety, tolerability, and comparative bioavailability of CTx-1301 (dexmethylphenidate) to the listed drug (Focalin XR™) under fasted conditions.

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Sponsor	Cingulate Therapeutics
Protocol Title:	A randomized, single-dose, four-sequence, four-period, in-clinic crossover study in adult ADHD subjects to establish safety, tolerability, and comparative bioavailability of CTx-1301 (dexmethylphenidate) to the listed drug (Focalin XR™) under fasted conditions.
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Role	Signatures	Date (dd-Mmm-yyyy)
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Document History

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Cingulate Therapeutics protocol number CTx-1301-001 (A randomized, single-dose, four-sequence, four-period, in-clinic crossover study in adult subjects with attention deficit and hyperactivity disorder (ADHD) to establish safety, tolerability, and comparative bioavailability of CTx-1301 (dexmethylphenidate) to the listed drug (Focalin XR™) under fasted conditions.), version 4.0, dated 16JAN2019. Reference materials for this SAP include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to the Cingulate Therapeutics study CTx-1301-001.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objectives

- To compare the bioavailability of the marketed product Focalin XR™ Extended-Release Capsules to the CTx-1301 trimodal product in a fasted state.
  - Demonstrate similar and comparative bioavailability of the highest dose of CTx-1301 (50 mg) to Focalin XR™ (40 mg) dose
  - Demonstrate similar and comparative bioavailability of the lowest dose of CTx-1301 (6.25 mg) to the lowest dose of Focalin XR™ (5 mg)
  - Demonstrate dose proportionality of CTx-1301 by evaluating the 6.25 mg dose to the 50 mg dose

2.1.2. Secondary Objectives

- To provide pharmacokinetic data on blood plasma levels of dexmethylphenidate (d-MPH)
- To evaluate the safety of CTx-1301 6.25 mg and 50 mg dose

2.1.3. Exploratory Objectives

- To further explore the impact of comparative bioavailability of the marketed product Focalin XR™ Extended-Release Capsules to the CTx-1301 trimodal product in a fasted state within selected time intervals

2.2. Study Endpoints

2.2.1. Primary Endpoints

- PK parameters including C_{max}, $AUC_{0-\infty}$, and AUC_{last}.

2.2.2. Secondary Endpoints

- PK plasma concentrations of d-MPH
- PK parameters including partial AUCs (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, and AUC_{12-16}) to examine potential differences between treatments (CTx-1301 6.25 mg vs. Focalin XR™ 5 mg and CTx-1301 50 mg vs. Focalin XR™ 40 mg) within selected time intervals.
- PK parameters including K, $T_{1/2}$, t_{max}, and t_{lag}.
- Safety measurements including ECG, vital signs, lab assessments, physical exam, and the incidence of treatment-emergent adverse events (TEAEs)

2.2.3. Exploratory Endpoints

- Additional exploratory analyses may be conducted to examine potential differences between treatments (CTx-1301 6.25 mg vs. Focalin XR™ 5 mg and CTx-1301 50 mg vs. Focalin XR™ 40 mg) within selected time intervals as needed

The exploratory endpoints will be evaluated post-hoc and described in the CSR.

3. Overall Study Design and Plan

3.1. Overall Design

This is a randomized, single-dose, four-sequence, four-period, in-clinic crossover study under fasted conditions. The study will involve approximately 36 adult ADHD study completers, male or female. The Screening period will occur from Day -28 to Day -5; subjects that meet eligibility at screening must washout of all stimulant medications at least 96 hours (hrs) prior to check in on Day -4. Subjects will remain in clinic from Day -4 to the end of study (EOS) visit at Day 10.

Subjects who complete screening, if eligible, will be brought back for the in-clinic portion of the study. Subjects will be reassessed for eligibility at check-in on Day -4 to ensure they still meet study criteria. Eligible Subjects will be in-clinic for the entire duration of the 15-day study (Day -4 to EOS at Day 10). Study visits include check-in day (Day -4), tolerability assessment (Day -3), Assessment 1 (Day 0), Assessment 2 (Day 3), Assessment 3 (Day 6), Assessment 4 (Day 9), and EOS (Day 10). Subjects that early terminate should follow the assessment structure of the EOS day; a final PK draw should be collected and labeled at early termination (ET) time. Additional unscheduled visits or assessments may be requested by an Investigator if concerned for subject

safety.

Subjects will be dosed with the following treatments according to a pre-defined, balanced, randomized crossover schedule:

Table 1: Study Treatments

Treatment A	Focalin XR™ Extended-Release capsule 5 mg
Treatment B	CTx-1301 trimodal 6.25 mg tablet
Treatment C	Focalin XR™ Extended-Release capsule 40 mg
Treatment D	CTx-1301 trimodal 50 mg tablet

Subjects will be randomized to sequences of treatment according to a 4×4 Williams design. Williams Design is a special case of Latin square design and is balanced for carryover effects.

Table 2: Study Design and Treatment Sequences

Sequence	**Period 1**	**Period 2**	**Period 3**	**Period 4**
1 (n = 9)	A	D	B	C
2 (n = 9)	B	A	C	D
3 (n = 9)	C	B	D	A
4 (n = 9)	D	C	A	B

Subjects must washout of all stimulant medications for a minimum of 96 hrs prior to check in on Day -4. Subjects must arrive at the clinic on Day -4 for check in (at least 12 hrs prior to receiving the test dose of 40mg Focalin XR™ at hr 0 on Day -3). Subjects may receive a snack (if needed) from hrs -12 to -10 on Day -4; at -10 hrs, all subjects must fast until at least hr 4 post-dose on Day -3. Water is restricted at least 1 hour (hr) prior to dosing and at least 2 hrs after dosing. An Investigator will assess if a subject has safely tolerated the 40mg dose of Focalin XR™ and can continue into the randomized portion of the study.

Subjects must fast from at least 10 hrs prior to dosing and at least 4 hrs post-dose on the test day and all Assessment Days (water is restricted at least 1 hr. prior to dosing and at least 2 hrs after dosing). Blood samples for pharmacokinetic analysis will be taken at the protocol-specified time points until 28 hrs post-dose (see Table 3). Vital signs (blood pressure and pulse) and ECG will be taken at the protocol-specified time points until 28 hrs post-dose.

Subjects will be discharged from the study center once they have completed all study assessments. The maximum period the subjects will be at the study center is approximately 15 days.

3.2. Sample Size and Power

The study design is a randomized, single-dose, four-sequence, four-period, in-clinic crossover study. C_{max}, $AUC_{0-\infty}$, and AUC_{last} are the key PK endpoints which will be used to evaluate the relative bioavailability of CTx-1301 6.25 mg vs. Focalin XR™ 5 mg (treatment B vs. treatment A) and CTx-1301 50 mg vs. Focalin XR™ 40 mg (treatment D vs. treatment C). The basis of evaluation for these endpoints will be 90% confidence intervals for the ratios of adjusted geometric means as described in Section 10.7 in protocol. In the context of a bioavailability analysis, similarity will be concluded if the 90% confidence interval (CI) of the geometric mean ratios for C_{max}, $AUC_{0-\infty}$, AUC_{last} fall near or within the 90% CI of [0.80–1.25]. This is the same as performing two one-sided hypothesis tests (TOST procedure), each conducted at a 5% significance level. The TOST procedure can identify two treatments as similar when the lower bound of a 90% confidence interval falls near or below 1.25 or the upper bound of a confidence interval falls near or above 0.80 (or both).

Based on the conservative TOST methodology assumption, that the bioavailability analysis falls within the 90% CI of [0.80, 1.25], a sample size of at least 32 evaluable subjects included in the PK Population, as described in Section 5, will provide at least 88% power with the assumption of within-subject coefficient of variation (CV) of 17-21% and true bioavailability ratio (B/A and D/C) of 93-107%. With assumption of the drop-out rate of 11%, approximately 36 completers will be randomized. No adjustment for multiple comparisons will be made.

3.3. Study Population

Approximately 36 study completers will be randomized in the study to achieve 32 evaluable subjects for the full study (at least 8 in each treatment sequence).

3.4. Treatments Administered

Subjects will be randomized to the 4 treatment sequences in Table 2 at the ratio of 1:1:1:1.

3.5. Method of Assigning Subjects to Treatment Sequences/Arms

This is a randomized study. Subjects should only be enrolled/randomized if they meet eligibility criteria both at screening and again at Day -4, Day -3, and Day -1.

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled/randomized to the study. Subject enrollment numbers will be assigned in ascending numerical order as enrolled. Subject randomization numbers will correspond to a pre-defined randomization schedule prepared by the Sponsor. Randomization numbers will be assigned in sequence across cohorts; replacement randomization numbers will be formatted in a manner similar to those initially assigned, but unique to the replacement patient.

There should be no sequence gaps in subject enrollment or initial randomization numbers. If a subject early terminates, then the assigned enrollment and randomization numbers must still remain attached to the early termination subject. If an initial randomization sequence is skipped, then the unblinded pharmacist must immediately consult with the unblinded statistician at the CRO for next steps.

An unblinded statistician may review the allocations to ensure the required number of completers (or evaluable PK Population patients) per treatment sequence was achieved as described in Section 3.2. This may be done after completion of a cohort and/or at the end of the study, depending on the number of dropouts and when they occur. Subjects which are not evaluable members of the

PK Population (Section 5) may be replaced if the required number of completers is not achieved for a sequence.

Any randomized subject that does not complete the study will be an early termination and reason for termination must be noted in the source document and eCRF.

3.6. Blinding and Unblinding

The unblinded pharmacy staff will prepare the study medications and maintain documentation of study drug administration for each subject according to the randomization schedule provided by the sponsor or sponsor representative/CRO. Verification by a second unblinded pharmacy member will be conducted to ensure the unblinded pharmacist has randomized the subject to the correct randomization sequence per the randomization schedule and instructions. The unblinded pharmacy staff must follow the site's pharmacy dispensing SOP. All doses will be administered from a blinded cup with a closed lid to prevent subjects from inspecting the tablets or capsules as well as to keep the subjects and study site staff blinded.

An unblinded statistician not involved in study conduct may review subject randomization allocations as described in Section 3.5.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 3.

Table 3: Schedule of Events

Procedure	Screening [a] (Day -28 to Day -5)	Clinic Check-In (Day -4)	Tolerability [c] Test (Day -3)	(Day -2)	(Day -1)	Assessment Days (Day 0, 3, 6, and 9)	Non-Assessment Days (Day 1, 2, 4, 5, 7, & 8)	EOS/ET[l] [l]	Unscheduled (USV)[m]
Written Informed Consent	✓								
Demographics	✓								
Medical History	✓	✓							
Current/Concomitant Medications	✓	✓	✓			✓		✓	
Inclusion & Exclusion Criteria	✓	✓	✓			✓[d]			
Wash-Out Call	✓[b]								
Physical Examination	✓	✓				✓[e]		✓	
MINI 7.0.2 version	✓								
C-SSRS	✓	✓	✓			✓		✓	
Electrocardiogram (ECG)	✓	✓	✓[f]			✓[f]		✓[f]	
Vital Signs	✓	✓	✓[g]			✓[g]	✓[g]	✓[g]	
Height	✓								
Weight	✓	✓						✓	
Serology	✓								
Clinical Safety Labs:									
Biochemistry	✓	✓						✓	
Hematology	✓	✓						✓	
Urinalysis	✓	✓						✓	
Serum HCG	✓[h]	✓[h]						✓[h]	
Urine Screen for Drugs of Abuse	✓	✓							
Breath Alcohol Test	✓	✓							
AE Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓

Procedure	Screening [a] (Day -28 to Day -5)	Clinic Check-In (Day -4)	Tolerability [c] Test (Day -3)	(Day -2)	(Day -1)	Assessment Days (Day 0, 3, 6, and 9)	Non-Assessment Days (Day 1, 2, 4, 5, 7, & 8)	EOS/ET[l] [l]	Unscheduled (USV)[m]
Ongoing Eligibility						✓		✓	
Test Dose of 40mg Focalin XR™			✓ c						
Randomization						✓ i			
Treatment Administration						✓ j			
PK Blood Sampling						✓ k		✓ k	

a: Screening day(s) will take place up to 24 days prior to Day -4 (check-in at clinic).
b. Washout call reminder should be completed 120 hrs (5 days) prior to Day -4. If subject is screened within the 120 hrs prior to Day -4, the washout call reminder is not required.
c. Tolerability day with Focalin XR 40 mg must occur on Day -3, allowing 3 days prior to Day 0 /Randomization to ensure washout of d-MPH. Dosing must occur before 8:30 am. If subject can't tolerate test dose, subject must be excluded.
d. Inclusion/Exclusion assessed at Screening, Day -4, and Day 0 prior to randomization; Eligibility continually assessed throughout study.
e. PE to occur mid-study on Day 6
f: ECG's administered on tolerability and Assessment days must be done prior to dosing, hr. 6, and hr. 28 (+/-30 min for post-dose ECGs).
g Vital signs will be taken prior to dosing and at 1 hr., 2 hr., 6 hr., and 28 hr. post-dose (+/- 10 minutes) at tolerability day (Day -3) and Days 0-9.
h. Serum HCG tests should be assessed in all women of child-bearing potential; Serum HCG should be assessed at Screening, check in on Day -4, and EOS.
i. Randomization will occur on Day 0 after ensuring subject still meets inclusion/exclusion criteria
j. Administration of study treatment must be separated by 3 days (72 hours). Administration of study treatments will occur on Day 0, Day 3, Day 6, and Day 9 before 8:30 am.
k. Blood samples for PK analysis will be taken pre-dose (0) -1 to 0 hr.) and post-dose at hrs. 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 24, and 28; if for ET visit, collect one last PK draw and record time of collection.
l. Early Termination (ET) day assessments should follow the EOS assessment schedule. If all assessments are not completed, note reason for noncompletion.
m. USV is at the discretion of an Investigator; USV will have no treatment administration or PK draws/analysis. All other assessments are at the discretion of the investigator.

4. Statistical Analysis and Reporting

All final, planned analyses identified in this SAP will be performed after the study database has been locked.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS® (release 9.4 or higher). All PK parameter estimations will be performed using Phoenix WinNonlin® version 8.0 or later. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in a particular category or each possible value. Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless stated otherwise, disposition and demographic characteristics data at baseline will be summarized overall, and by treatment sequence, while safety and PK data will be presented by treatment group and period/visit (e.g. reported within the treatment group associated with the scheduled visit), unless otherwise specified. The EOS/ET visit will be displayed based on the last treatment group received by a subject.

A subject must have been dosed with drug in a specified period in order to be included in the reporting for that period; data will be analyzed based on the treatment received for a specified period.

4.2. Interim Analysis and Data Monitoring

No interim analyses or Data Monitoring Committee are planned.

An unblinded analysis of the randomization and disposition data will be performed as described in Section 3.5. Since the review will be performed by an unblinded statistician with no involvement in study activities for purposes of ensuring the planned enrollment requirements have been satisfied, there will be no statistical penalty for this review.

5. Analysis Populations

The following analysis populations are planned for this study:

- **All Enrolled Subjects (ITT):** Includes all intent-to-treat (ITT) subjects who have signed the informed consent form (ICF), meet the eligibility criteria, and are randomized to a

treatment sequence. This population will be used for subject disposition and protocol deviation summaries and listings.

- **Safety Population (SAF):** The Safety Population includes all enrolled subjects who receive at least 1 dose of study drug. The SAF will be used for demographics and other baseline characteristic summaries and listings, for analyses of all safety endpoints, and for the exposure listing.
- **Pharmacokinetic (PK) Population:** The PK Population includes all subjects who receive at least 1 dose of study drug and provide at least 1 evaluable PK plasma concentration. The PK Population will be used for all PK analyses.

6. Statistical Definitions and Algorithms

6.1. Baseline

The last observation recorded prior to the first dose will be used as the baseline, or to derive the baseline in summaries of demographic and baseline characteristics. Baseline of clinical laboratory evaluations, physical examinations, and the Columbia Suicide Severity Rating Scale (C-SSRS) is the last observation prior to the first dose of study medication.

The last observation prior to dose of treatment at each treatment period (pre-dose time point) will be used as the baseline observation of that treatment period in calculating changes from baseline of vital signs, ECGs and PK concentrations.

6.2. Adjustments for Covariates

Additional variables may be explored in post hoc analyses if deemed appropriate; additional covariate analyses will be described in CSR. Adverse event and ECGs will report selected summaries by cigarette smoking status (non-current smokers, current smokers); additional analyses may be performed as appropriate.

6.3. Multiple Comparisons

No adjustments will be made for multiple comparisons.

6.4. Handling of Dropouts or Missing Data

Approximately 36 subjects will be randomized in order to achieve the target of 32 evaluable subjects (at least 8 in each treatment sequence) completing the entire study. Subjects that early terminate may be replaced at the discretion of the Sponsor. All subjects treated with at least one dose will be in the SAF. All subjects who receive at least one study treatment and complete at least one PK blood draw will be included in PK analyses.

Back-up subjects may be recruited to the site on Day -4 in case of screen failures. The study will be conducted in approximately 4-5 cohorts. After completion of each cohort, randomization data may be reviewed by an unblinded statistician as described in Section 3.5.

There will be no data imputation for PK or safety endpoints.

6.5. Analysis Visit Windows

In general, summary tables of all variables for this study will use the nominal time point as collected in the eCRF/database. An exception to this is the derivation of baseline as defined in Section 6.7. Baseline values will be based on all assessments, whether scheduled or unscheduled. Unscheduled visits will be presented in data listings.

6.6. Pooling of Sites

No pooling of sites will be conducted; there is only one site in the study.

6.7. Derived Variables

- Age (years) at Baseline = Integer of (Day 0 visit date – Date of Birth) / 365.25
- Study Day = Assessment Day – Date of First Dose (Day 0)
- Body Mass Index (BMI) = (Weight (kg) / (Height $(cm)^2$) x 10,000
- Change from baseline = value at current time point – value at baseline
- TEAE = any adverse event (AE) with an onset date on or after the first dose of study medication on Day 0 after randomization
- Medications which continue or start after the first administration of study medication on Day 0 will be considered concomitant.

6.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Adverse events will be coded using the MedDRA version 22.0 dictionary.

A treatment-related AE is any AE identified as “Related to study drug” in the eCRF; procedure related AEs are those which are identified as “Procedure related” in the eCRF.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

Prior to any imputation, given the multiple treatments administered in this study, dates will be queried to make all attempts at completeness in order to ensure reporting coincides with the appropriate treatment period for the subject.

7. Study Subjects and Demographics

All demographic and baseline summaries including disposition, demographic and baseline characteristics, medical history, and prior medication will be presented overall (all treatment sequences), and by treatment sequence for All Enrolled Subjects, SAF, and PK Populations, as needed.

Concomitant medication and study drug exposure will be summarized by treatment group and period for the SAF. Concomitant medications will additionally be summarized by treatment group over all periods, as described in Section 7.5.

7.1. Disposition of Subjects and Withdrawals

The number and percentage of subjects included in each analysis population, who complete the study, who complete each period, who receive each treatment, and who early terminate from treatment at any time during the study will be tabulated by treatment sequence and overall for All Enrolled Subjects (ITT).

A by-subject enrollment and disposition listing will be presented for All Enrolled Subjects.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed for All Enrolled Subjects.

7.3. Demographics and Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, cohort, height, weight, BMI, and cigarette smoking status at baseline will be presented overall, and by treatment sequence based on All Enrolled Subjects (ITT), SAF, as well as for the PK Populations.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median, and maximum will be tabulated. For the categorical variables, counts and proportions of each value will be presented.

Demographic and other baseline characteristics will be presented in subject listings for All Enrolled Subjects.

7.4. Medical History

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v. 22.0), will be tabulated overall and by treatment sequence. If a subject has multiple records under the same System Organ Class (SOC) and preferred term, only one will be counted. This analysis will be conducted for the SAF.

By-subject listings of all medical history will be presented for the SAF.

7.5. Prior and Concomitant Medication

Prior medications will be presented separately from concomitant medications. Medications will be coded using WHO-DD v. March 1, 2019 and reported in Anatomical Therapeutic Chemical (ATC) Level 4.

Medications that started prior to the first administration of study drug on Day 0 will be considered prior medications whether or not they were stopped prior to first administration of study medication. Prior medications will be summarized descriptively with counts and percentages overall, and by treatment sequence for the SAF.

Any medications continuing or starting post the first administration of study medication on Day 0 will be considered to be concomitant. Concomitant medications will be summarized by treatment group (including All CTx-1301 and All Focalin XR™ groups) and period, based on the time that concomitant medication continues or starts. Concomitant medication will be assigned to a treatment period if the start date and time is on or after the drug administration date and time of that treatment period, and before the drug administration date and time of the next treatment period. In the case that a single medication belongs to more than one treatment period, the medication will be counted in all treatment groups (including All CTx-1301 and All Focalin XR™ groups)/periods it falls into. Concomitant medications will additionally be summarized by treatment group (including All CTx-1301 and All Focalin XR™ groups) over all periods.

If a medication starts prior to the first administration of study medication on Day 0 and continues after that, it will be considered both prior and concomitant. Subjects will be counted only once for each Anatomical Therapeutic Chemical (ATC) and Preferred Term in each treatment sequence or group column. A by-subject listing of all prior and concomitant medications will be presented for the SAF.

7.6. Exposure and Compliance

Exposure to each of the four treatments on Day 0, 3, 6, and 9 will be summarized by treatment group (including All CTx-1301 and All Focalin XR™ groups) and overall for the SAF. Individual data listings will be provided for the SAF. A separate listing will be provided for the tolerability test on Day -3.

8. Pharmacokinetic Analysis

Unless otherwise stated, all PK analyses will be created using the PK Population.

Plasma Concentrations

Individual plasma concentration vs actual time data will be used to estimate the PK parameters by standard non-compartmental methods for each subject in the PK population, as data permit.

For plasma concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. Individual plasma concentrations of d-MPH will be summarized by treatment group at each time point using descriptive statistics. Individual concentration plots and mean data graphs will be produced. All graphs will be presented using both linear and semi-logarithmic scales.

Pharmacokinetic Parameters

Pharmacokinetic parameter estimation will be performed using the individual plasma concentration-time data. The actual elapsed times will be used for all calculations. For the PK parameter calculation, BLQ plasma concentrations occurring before T_{max} will be set to 0, with the exception of a BLQ value occurring between two measurable concentrations, in which case it will be set to missing. BLQ plasma concentrations occurring after T_{max} will be set to missing. Pharmacokinetic parameter estimates and summaries will be completed for subjects in the PK population having sufficient measurable concentrations to define the PK profile. $AUC_{0-\infty}$ values for which the extrapolated part exceeds 20% of the total AUC will be excluded from the calculation of the descriptive statistics. No value for $AUC_{0-\infty}$, k_{el}, and t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time data.

Pharmacokinetic parameter estimates will be summarized by treatment group using descriptive statistics, including arithmetic and geometric means, SD, % CV, median, minimum, and maximum. For T_{max} and T_{lag}, only the median and the range will be reported.

8.1. Analysis on Primary PK Endpoints

8.1.1. Primary PK Analysis

The primary PK analysis will be based on PK parameters including C_{max}, $AUC_{0-\infty,}$ and AUC_{last}.

The three natural log-transformed PK parameters (including C_{max}, $AUC_{0-\infty,}$ and AUC_{last}) will be summarized descriptively by treatment group and compared between treatment groups (CTx-1301 6.25 mg vs. Focalin XR™ 5 mg and CTx-1301 50 mg vs. Focalin XR™ 40 mg) using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (CTx-1301 6.25 mg vs. Focalin XR™

5 mg and CTx-1301 50 mg vs. Focalin XR™ 40 mg) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Treatment B/A and Treatment D/C) and 90% CIs for the ratios. The resulting CIs will be compared to an acceptability region of [0.80, 1.25], which is equivalent to performing two one-sided hypothesis tests (TOST procedure), each conducted at a 5% significant level. The two treatments will be identified as similar with comparative bioavailability when the 90% CI falls near or inside [0.80, 1.25].

Natural log-transformed, dose-normalized PK parameters (including C_{max}, $AUC_{0-\infty,}$ and AUC_{last}) will also be calculated (by dividing the nominal dose) and summarized similarly. Dose proportionality will also be evaluated based on the model for dose-normalized parameters, using a ratio of adjusted geometric means (Treatment C/B) for comparison of the CTx-1301 50 mg and CTx-1301 6.25 mg groups, along with corresponding 90% confidence intervals.

8.1.2. Sensitivity Analysis on Primary PK Endpoints

A sensitivity analysis may be conducted to evaluate any cohort effect on the primary PK endpoints (including C_{max}, $AUC_{0-\infty,}$ and AUC_{last}). Sensitivity analysis will be done on both natural log-transformed and natural log-transformed, dose-normalized PK parameters.

Cohort at enrollment will be added as a random effect into the mixed-effect model for primary PK analysis as described in Section 8.1.1. Estimates of adjusted mean differences and corresponding 90% CIs will be obtained from the model and will be exponentiated to provide estimates of the ratios of adjusted geometric means and 90% CIs for the ratios.

All plasma concentration parameters will be presented in a data listing.

8.2. Analysis on Secondary PK Endpoints

8.2.1. Secondary PK Analysis

PK plasma concentrations of d-MPH

Plasma concentration data of d-MPH will be analyzed as described in Section 8. All plasma concentration data will be presented in a data listing.

PK parameters (partial AUCs)

PK parameters including partial AUCs (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, and AUC_{12-16}) to examine potential differences between treatments (CTx-1301 6.25 mg vs. Focalin XR™ 5 mg and CTx-1301 50 mg vs. Focalin XR™ 40 mg) within selected time intervals will be summarized similarly as primary analysis described in Section 8.1.

PK parameters (K, $T_{1/2}$, t_{max}, and t_{lag})

PK parameters including K and $T_{1/2}$ will be summarized descriptively by treatment group. For t_{max} and t_{lag}, the median and the range (minimum, maximum) will be reported.

All PK parameter data will be presented in a data listing.

8.2.2. Sensitivity Analysis on Secondary PK Endpoints

A sensitivity analysis may be conducted to evaluate any cohort effect on the secondary PK endpoints (partial AUCs). Sensitivity analysis may also be conducted on the log-transformed and natural log-transformed dose-normalized PK parameters.

Cohort at enrollment will be added as a random effect into the mixed-effect model for secondary PK analysis as described in Section 8.2.1. Estimates of adjusted mean differences and corresponding 90% CIs will be obtained from the model and will be exponentiated to provide estimates of the ratios of adjusted geometric means and 90% CIs for the ratios.

9. Safety and Tolerability Analysis

Safety analyses will be based on the SAF. Safety will be assessed by clinical review of all relevant safety data including treatment-emergent adverse events (TEAEs), clinical laboratory tests, physical exams, vital signs, ECGs, and C-SSRS. No inferential testing for statistical significance will be performed.

All safety presentations will be based on the SAF.

9.1. Adverse Events

All AEs, TEAEs, and serious adverse events (SAEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) classification system. TEAE is defined as any adverse event with an onset date on or after the first dose of study medication on Day 0 after randomization.

Adverse events are considered treatment emergent for a period if the event begins at the time of or after drug administration for a specified period; events are reported based on the treatment received during a specified period. Subjects are counted only once within a specified period for each category of reporting (e.g. system organ class [SOC] and preferred term [PT]). TEAE incidences will be reported by period and treatment group (including All CTx-1301 and All Focalin XR™ groups), as well as over all periods by treatment group.

An overall summary of treatment emergent adverse event will be provided, which includes the number and percentage of subjects who experience at least one: TEAE (and by maximum severity); treatment related TEAE; procedure related TEAE; TEAE related to study or drug withdrawal; treatment-emergent serious adverse event (TESAE); TESAE related to study drug; TESAE related to procedure; and a TEAE leading to death. This summary will be reproduced by cigarette smoking status.

The number and percent of subjects reporting TEAEs, grouped by MedDRA system organ class (SOC) and preferred term (PT) will be tabulated by severity, and relationship to treatment. Subjects will be counted only once for each SOC and PT in each treatment period. Such summaries will be displayed for the following:

- TEAEs by SOC and PT (also produced by cigarette smoking status)

- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to treatment
- TEAEs leading to death by SOC and PT
- Treatment-emergent SAEs (TESAEs) by SOC and PT
- AEs leading to study or drug withdrawal by SOC and PT

In the summaries showing severity and relationship to treatment the event with the maximum severity or strongest relationship will be reported. For example, if a particular event is missing the severity, then the strongest possible severity will be assumed for analysis (severity = severe).

In the AE data listings, all AEs will be displayed and TEAEs will be flagged.

9.1.1. Adverse Events Leading to Study or Drug Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug by treatment group, period, SOC, and PT will be prepared. As described in Section 9.1, these events will also be summarized by period and treatment group (including All CTx-1301 and All Focalin XR™ groups), as well as over all periods by treatment group.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

All TESAEs will be listed and also tabulated by SOC and PT and presented by treatment group (including All CTx-1301 and All Focalin XR™ groups) and period. As described in Section 9.1, these events will also be summarized by period and treatment group, as well as over all periods by treatment group.

9.2. Clinical Laboratory Evaluations

Descriptive summaries of actual (absolute) values and changes from baseline to EOS/ET visit will be presented for each clinical laboratory analyte (including biochemistry, hematology and urinalysis) by treatment group (including All CTx-1301 and All Focalin XR™ groups) based on the last treatment received prior to the EOS/ET visit and overall for the SAF. Baseline values will be presented in aggregate over all participants.

The number and percentage of subjects with clinical laboratory values below, within, or above the normal range and the shift from baseline to EOS/ET visit will be tabulated for each clinical laboratory analyte by treatment group as defined above and overall for the SAF.

By-subject listings of laboratory analytes will be presented for the SAF. Any out-of-range values that are identified by the investigator as being clinically significant will be flagged as high, low, or out-of-range on this listing. Pregnancy, urine drug screens, and breath alcohol test results will also be listed. Pregnancy test includes serum pregnancy tests, which are collected and will be analyzed in women of child-potential only.

9.3. Physical Examination

Physical exam results will be summarized descriptively by treatment group (including All CTx-1301 and All Focalin XR™ groups) and overall by visit for the SAF, where the number and percentages of subjects with abnormal findings will be tabulated for each test. Visits will be displayed based on the last treatment received prior to evaluation. Baseline values will be presented in aggregate over all participants.

A by-subject listing of abnormal findings will be provided with clinical significance being indicated.

9.4. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure and heart rate measured pre- and post-dose on Days 0, 3, 6 and 9, and presented by treatment group (including All CTx-1301 and All Focalin XR™ groups) and overall by nominal sampling time point during each treatment period and over all periods for the SAF. The EOS/ET visit will be presented based on the last treatment received prior to study completion/discontinuation.

By-subject listing of all vital sign measurements including height, weight and BMI will be presented.

9.5. Electrocardiograms (ECG)

Descriptive summaries of actual values and changes from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF, and ventricular rate measured pre- and post-dose on Days 0, 3, 6 and 9, and presented by treatment group (including All CTx-1301 and All Focalin XR™ groups) and overall by nominal sampling time point during each treatment period and over all periods for SAF. The EOS/ET visit will be presented based on the last treatment received prior to study completion/discontinuation.

The number and percentage of subjects with normal and abnormal ECG results will be summarized by visit for the SAF as described above. This summary will also be reported by cigarette smoking status.

A by-subject listing of all ECG measures and incidences of abnormalities will be presented.

9.6. Columbia Suicide Severity Rating Scale (C-SSRS)

A summary of incidence (counts and percentages) of suicidal ideation and behavior will be presented by treatment group (including All CTx-1301 and All Focalin XR™ groups) and overall by visit for the SAF. Visit data, including the EOS/ET visit, will be displayed based on the last treatment received prior to evaluation. Baseline values will be presented in aggregate over all participants. All incidences of suicidal ideation and behavior collected on the C-SSRS will be listed by subject.

9.7. MINI International Neuropsychiatric Interview (M.I.N.I.)

The M.I.N.I. summary responses at screening visit will be listed by subject. M.I.N.I. version 7.0.2 will be used.

10. References

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

11. Tables, Listings, and Figures

All tables, listings, and figures will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (listing number) with a run date and time stamp.

Labels for Treatment Sequences and Treatment Groups:

All the TLF will be using "Sequence 1, 2, 3, 4" and "Treatment A, B, C, D" with reference to the treatment sequences and treatment groups as described in Section 3.1, Table 1 and Table 2. In draft and final TLF outputs, the following general footnote will be added appropriately to specify complete treatment sequences information and treatment names. ***General footnote for every output:***

Note: This is a randomized, single-dose, four-sequence, four-period crossover study. Sequence 1 = ADBC, Sequence 2 = BACD, Sequence 3 = CBDA, Sequence 4 = DCAB where A = Focalin XR™ Extended-Release capsule 5 mg; B = CTx-1301 trimodal 6.25 mg tablet; C = Focalin XR™ Extended-Release capsule 40 mg; D = CTx-1301 trimodal 50 mg tablet.

Additional information: If a note already exists on an output as "Note," include this information first and ensure "Note" is relabeled "Notes."

For selected Section 14.1 (noted when needed) and 14.3 (assumed all) tables, additional columns will be included to accommodate All CTx-1301, All Focalin XR™ (and some of these also include Overall)reporting in addition to the Treatment A, B, C, or D. Please see programming notes as to when these additional columns are needed. They will be added in the order specified on the right side of the reporting table.

General Reporting Conventions:

- All tables and data listings will be developed in landscape orientation using Times New Roman font.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g. μ, α, β).
- In the header, the sponsor's company name and protocol will be left justified at the top of the page. Page x of y (total number of pages), indicating page number, will be right justified at the top of the page.
- All titles will be centered on a page. The ICH numbering convention is to be used for all outputs.
- All footnotes will be left justified and at the bottom of a page.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A value of zero may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as ddmmmyyyy (e.g., 29AUG2011) format. A 4-digit year is preferred for all dates.
- If applicable, all observed time values will be presented by using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the sample size (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed, however counts and percentages of missing values may be needed.
- All population summaries for continuous variables will include: N, mean, median, standard deviation (SD), minimum, and maximum. Other summaries (e.g., number missing or CV%) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x %). A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a 0.

11.1. Planned Table Descriptions

The following are planned summary tables for protocol number CTx-1301-001. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table Number	Population	Table Title
14.1 Demographics and Baseline Tables		
14.1.1	All Enrolled	Study Populations and Subject Disposition
14.1.2.1	All Enrolled	Demographics and Baseline Characteristics
14.1.2.2	SAF	Demographics and Baseline Characteristics
14.1.2.3	PK Population	Demographics and Baseline Characteristics
14.1.3.1	SAF	Medical History
14.1.3.2	SAF	Prior Medication
14.1.3.3	SAF	Concomitant Medication
14.1.4	SAF	Summary of Drug Exposure
14.2 PK Tables		
14.2.1.1	PK Population	Primary PK Analysis of Natural log-transformed PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last}) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.1.1.1	PK Population	Sensitivity Analysis on Primary PK Endpoints: Natural log-transformed PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last}) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.1.1.2	PK Population	Primary PK Analysis of Natural log-transformed PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last}) Summary of Descriptive Statistics
14.2.1.2	PK Population	Primary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last}) Summary of Estimates of Mean Differences between Treatments and Dose Levels from Mixed Effect Model
14.2.1.2.1	PK Population	Sensitivity Analysis on Primary PK Endpoints: Natural log-transformed, Dose-normalized PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last}) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.1.2.2	PK Population	Primary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last}) Summary of Descriptive Statistics
14.2.2.1	PK Population	Secondary PK Analysis of Natural log-transformed PK Parameters (Partial AUCs) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.2.1.1	PK Population	Sensitivity Analysis on Secondary PK Endpoints: Natural log-transformed PK Parameters (Partial AUCs) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.2.1.2	PK Population	Secondary PK Analysis of Natural log-transformed PK Parameters (Partial AUCs) Summary of Descriptive Statistics

14.2.2.2	PK Population	Secondary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (Partial AUCs) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.2.2.1	PK Population	Sensitivity Analysis on Secondary PK Endpoints: Natural log-transformed, Dose-normalized PK Parameters (Partial AUCs) Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
14.2.2.2.2	PK Population	Secondary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (Partial AUCs) Summary of Descriptive Statistics
14.2.2.3	PK Population	Secondary PK Analysis of Natural log-transformed PK Parameters (K and $T_{1/2}$) Summary of Descriptive Statistics
14.2.2.4	PK Population	Secondary PK Analysis of PK Parameters (t_{max} and t_{lag}) Summary of Descriptive Statistics
14.2.2.5	PK Population	Secondary PK Analysis: Summary of Plasma Concentration of d-MPH
14.3 Safety and Tolerability Tables		
14.3.1 Displays of Adverse Events		
14.3.1.1.1	SAF	Summary of all TEAEs
14.3.1.1.2	SAF	Summary of all TEAEs, Non-Current Cigarette Smokers
14.3.1.1.3	SAF	Summary of all TEAEs, Current Cigarette Smokers
14.3.1.2.1	SAF	TEAEs by SOC and Preferred Term
14.3.1.2.2	SAF	TEAEs by SOC and Preferred Term, Non-Current Cigarette Smokers
14.3.1.2.3	SAF	TEAEs by SOC and Preferred Term, Current Cigarette Smokers
14.3.1.3	SAF	TEAEs by SOC, Preferred Term and Severity
14.3.1.4	SAF	TEAEs by SOC, Preferred Term and Relationship to Treatment
14.3.1.5	SAF	TEAEs leading to Death by SOC and Preferred Term
14.3.1.6	SAF	TESAEs other than Death by SOC and Preferred Term
14.3.1.7	SAF	AEs leading to Premature Discontinuation by SOC and PT
14.3.2 Laboratory Safety Data		
14.3.2.1	SAF	Summary of Biochemistry by Treatment
14.3.2.2	SAF	Summary of Hematology by Treatment
14.3.2.3	SAF	Summary of Urinalysis by Treatment
14.3.2.4	SAF	Biochemistry Shift from Baseline to EOS/ET Visit
14.3.2.5	SAF	Hematology Shift from Baseline to EOS/ET Visit
14.3.2.6	SAF	Urinalysis Shift from Baseline to EOS/ET Visit
14.3.3 Physical Examination Data		
14.3.3.1	SAF	Summary of Physical Examination by Treatment
14.3.4 Vital Signs and ECG Data		
14.3.4.1	SAF	Summary of Vital Signs by Treatment
14.3.5.1	SAF	Summary of ECG Parameters by Treatment
14.3.5.2.1	SAF	Incidence of Investigator ECG Interpretation by Treatment
14.3.5.2.2	SAF	Incidence of Investigator ECG Interpretation by Treatment, Non-Current Cigarette Smokers
14.3.5.2.3	SAF	Incidence of Investigator ECG Interpretation by Treatment, Current Cigarette Smokers
14.3.6.1	SAF	C-SSRS, Incidence of Ideation/Behavior by Treatment

11.2. Planned Figure Descriptions

The following are planned figures for protocol number CTx-1301-001. The table numbers are place holders only and will be determined when the tables are produced.

Figure Number	Population	Figure Title
14.2 PK Figures		
14.2.4.1	PK Population	Individual Plasma Concentration of d-MPH Scatterplot (linear)
14.2.4.2	PK Population	Individual Plasma Concentration of d-MPH Scatterplot (semi-logarithmic)
14.2.4.3	PK Population	Mean Plasma Concentration of d-MPH vs. Time by Treatment (linear)
14.2.4.4	PK Population	Mean Plasma Concentration of d-MPH vs. Time by Treatment (semi-logarithmic)

11.3. Planned Listing Descriptions

The following are planned data and subject data listings for protocol number CTx-1301-001.

In general, one listing will be produced per CRF domain. All listings will be sorted by planned treatment sequence and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (eg, repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Listing Number	Population	Listing Title
16.2.1 Subject Disposition		
16.2.1.1	All Enrolled	Study Populations and Disposition
16.2.1.2	All Enrolled	Randomization and Treatment Completion
16.2.2 Protocol Deviations		
16.2.2.1	All Subjects	Inclusion and Exclusion Criteria
16.2.2.2	All Enrolled	Protocol Deviations
16.2.4 Demographics and Other Baseline Characteristics		
16.2.4.1	All Enrolled	Demographics
16.2.4.2	SAF	Medical History
16.2.4.3	SAF	Prior and Concomitant Medication
16.2.4.4	SAF	Cigarettes Smoking Log
16.2.5 Drug Exposure		
16.2.5.1	SAF	Study Drug Administration
16.2.5.2	SAF	Tolerability Drug Administration
16.2.6 Efficacy and PK Listings (PK Concentration)		
16.2.6.1	PK	Plasma concentration of d-MPH
16.2.6.2	PK	PK Parameters
16.2.7 Adverse Event Listings		
16.2.7.1	SAF	All Adverse Events
16.2.7.2	SAF	Serious Adverse Events
16.2.7.3	SAF	Adverse Events leading to Discontinuation
16.2.7.4	SAF	Listing of Deaths
16.2.8 Laboratory Data Listings		
16.2.8.1	SAF	Biochemistry
16.2.8.2	SAF	Hematology
16.2.8.3	SAF	Urinalysis
16.2.8.4	SAF	Thyroid
16.2.8.5	SAF	Urine Drug Screen
16.2.8.6	SAF	Serology
16.2.8.7	SAF	Pregnancy
16.2.8.8	SAF	Breath Alcohol Test
16.2.9 Other Clinical Observations and Measurements		
16.2.9.1	SAF	Physical Examination
16.2.9.2	SAF	Vital Signs
16.2.9.3	SAF	Electrocardiogram (ECG)
16.2.9.4	SAF	C-SSRS
16.2.9.5	SAF	M.I.N.I.

12. Tables, Listings, and Listing Shells

12.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

Standardized Layout

Cingulate Therapeutics, Inc — Page xx of xx
Protocol: CTx-1301-001 — <Version>

<Table, Listing, Figure> xx.x.x

<Title of Table Listing or Figure>

<Study Population and if applicable subgroup Description>

Body of Table, Listing or Figure

<Note: If directly Applicable>
Footnote 1 *<if applicable>*
Footnote 2 *<if applicable>*
Footnote n *<if applicable>*
Source: Listing xx.x.x, xx.x.x *<if applicable>*
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

12.2. Planned Table Shells

Table 14.1.1
Study Populations and Subject Disposition
All Enrolled Subjects (ITT)

Status or Variable/Statistic	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
All Enrolled Subjects [1]	xx	xx	xx	xx	xx
Safety Population (SAF) [2]	xx	xx	xx	xx	xx
Pharmacokinetic (PK) Population [3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Completed Study	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Early Termination	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for Early Termination [4]					
Withdrawal by subject	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal lab test result	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Protocol deviation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-compliance with study restrictions	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Administrative reasons	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Unless otherwise stated, percentages are based on the number of subjects in the SAF Population. Planned treatment sequences are presented.
[1] All Enrolled Subjects includes all subjects who have signed the informed consent form, meet eligibility criteria, and are randomized to a treatment sequence.
[2] The Safety Population (SAF) includes all subjects who receive at least 1 dose of study drug.
[3] The Pharmacokinetic (PK) Population includes all subjects who receive at least 1 dose of study drug and provide at least one evaluable PK plasma concentration.
[4] Percentages are based off of number of early terminations per applicable treatment column.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.1.1 (Continued)
Study Populations and Subject Disposition
All Enrolled Subjects (ITT)

Status or Variable/Statistic	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
Period Completion					xx
Period 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment Completion					
Treatment A	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment B	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Treatment D	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Unless otherwise stated, percentages are based on the number of subjects in the SAF Population. Planned treatment sequences are presented.
[1] All Enrolled Subjects includes all subjects who have signed the informed consent form, meet eligibility criteria, and are randomized to a treatment sequence
[2] The Safety Population (SAF) includes all subjects who receive at least 1 dose of study drug.
[3] The Pharmacokinetic (PK) Population includes all subjects who receive at least 1 dose of study drug and provide at least one evaluable PK plasma concentration.
[4] Percentages are based off of number of early terminations per applicable treatment column.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.1.2.1
Demographics and Baseline Characteristics
All Enrolled Subjects (ITT)

Variable Statistics or Category	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
Age (years)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Gender					
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ethnicity					
Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Race					
American Indian/Alaska Native	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Asian	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Black or African American	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Native Hawaiian or Other Pacific Islander	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N. Planned treatment sequences are presented.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.1.2.1 (Continued)
Demographics and Baseline Characteristics
All Enrolled Subjects (ITT)

Variable Statistics or Category	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
Height (cm)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Weight (kg)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
BMI (kg/m2)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Note: Percentages are 100*n/N. Planned treatment sequences are presented.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.1.2.1 (Continued)
Demographics and Baseline Characteristics
All Enrolled Subjects (ITT)

Variable Statistics or Category	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
Cohort					
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
..					
Cigarette Smoking Status					
Current Cigarette Smoker	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Former Cigarette Smoker	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Never Smoked Cigarettes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N. Planned treatment sequences are presented.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming Note: Check with the biostatistician as to the number of cohorts required; only report up to the number of cohorts actually used in the study.

Table 14.1.2.2
Demographics and Baseline Characteristics
Safety Population
{Programming note: Repeat 14.1.2.1 with Safety Population}

Table 14.1.2.3
Demographics and Baseline Characteristics
PK Population
{Programming note: Repeat 14.1.2.1 with PK Population}

Table 14.1.3.1
Medical History
Safety Population

System Organ Class [1] Preferred Term	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
Number of subjects with at least one medical history event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…					

Note: Percentages are 100*n/N. Planned treatment sequences are presented. Subjects are counted only once for each System Organ Class and Preferred Term. Coded terms have been displayed alphabetically by System Organ Class and similarly by Preferred Term within System Organ Class.
[1] Medical History is coded using MedDRA version 22.0.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.1.3.2
Prior Medication
Safety Population

ATC [1] Preferred Term	Sequence 1 (N=xx)	Sequence 2 (N=xx)	Sequence 3 (N=xx)	Sequence 4 (N=xx)	Overall (N=xx)
Number of subjects with at least one prior medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…					

Note: Percentages are 100*n/N. Planned treatment sequences are presented. Subjects are counted only once for each Anatomical Therapeutic Chemical (ATC) and Preferred Term. A prior medication is any medication that started prior to the first administration of study drug on Day 0 whether or not they were stopped prior to first administration of study medication. Medications are displayed alphabetically by ATC and similarly by Preferred Term within ATC.
[1] Prior Medication is coded using WHO-DD v. March 1, 2019.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.1.3.3
Concomitant Medication
Safety Population

ATC [1] Preferred Term	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
All Periods	xx	xx	xx	xx
Number of subjects with at least one concomitant medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…				

{Programming notes: Repeat for Period 1, 2, 3, 4 respectively}

Note: Percentages are based on the number of subjects treated within the specified period. A concomitant medication is any medications continuing or starting after drug administration within the specified period. In the case that a single medication belongs to more than one treatment period, the medication will be counted in all treatment groups/periods it falls into. Subjects are counted only once for each Anatomical Therapeutic Chemical (ATC) and Preferred Term. Medications are displayed alphabetically by ATC and similarly by Preferred Term within ATC.
[1] Concomitant Medication is coded using WHO-DD v. March 1, 2019.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: Each period must display a denominator. This denominator will represent the number of patients treated in each period. This table is one selected in this section (14.1) which needs to have the All CTx-1301 and All Focalin™ columns added.

Table 14.1.4
Summary of Drug Exposure
Safety Population

Period (Treatment Day)	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
Period 1 (Day 0)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 2 (Day 3)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 3 (Day 6)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 4 (Day 9)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This table is one selected in this section (14.1) which needs to have the All CTx-1301, All Focalin™, and Overall columns added.

Table 14.2.1.1
Primary PK Analysis of Natural log-transformed PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last})
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population

Parameter	Treatment Effect	Adjusted Geometric Mean (90% CI)/ Ratio (90% CI)	Treatment Effect	Adjusted Geometric Mean (90% CI)/ Ratio (90% CI)	*Dose Proportionality*	*Adjusted Geometric Mean (90% CI)/ Ratio (90% CI)*
C_{max}	Treatment A	xx.x (xx.xx, xx.xx)	Treatment C	xx.x (xx.xx, xx.xx)		
	Treatment B	xx.x (xx.xx, xx.xx)	Treatment D	xx.x (xx.xx, xx.xx)		
	Treatment B/A	xx.x (xx.xx, xx.xx)	Treatment D/C	xx.x (xx.xx, xx.xx)	*Treatment C/B*	*xx.x (xx.xx, xx.xx)*
$AUC_{0-\infty}$	Treatment A	xx.x (xx.xx, xx.xx)	Treatment C	xx.x (xx.xx, xx.xx)		
	Treatment B	xx.x (xx.xx, xx.xx)	Treatment D	xx.x (xx.xx, xx.xx)		
	Treatment B/A	xx.x (xx.xx, xx.xx)	Treatment D/C	xx.x (xx.xx, xx.xx)	*Treatment C/B*	*xx.x (xx.xx, xx.xx)*
AUC_{last}	Treatment A	xx.x (xx.xx, xx.xx)	Treatment C	xx.x (xx.xx, xx.xx)		
	Treatment B	xx.x (xx.xx, xx.xx)	Treatment D	xx.x (xx.xx, xx.xx)		
	Treatment B/A	xx.x (xx.xx, xx.xx)	Treatment D/C	xx.x (xx.xx, xx.xx)	*Treatment C/B*	*xx.x (xx.xx, xx.xx)*

Note: Estimates of adjusted mean differences and corresponding 90% confidence intervals are estimated from a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect and natural log-transformed PK parameter as responding variable. The estimated adjusted mean differences and 90% confidence intervals are exponentiated to provide estimates of the ratio of adjusted geometric means and 90% confidence intervals for the ratios.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: Dose proportionality will only appear in Table 14.2.1.2 only (this is why it is italicized). It is not planned to be presented in all tables of this type.

Table 14.2.1.1.1
Sensitivity Analysis on Primary PK Endpoints: Natural log-transformed PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last})
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population
{Programming Note: Repeat Table 14.2.1.1 by changing the model and footnote.}

Note: Estimates of adjusted mean differences and corresponding 90% confidence intervals are estimated from a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence and cohort as random effects and natural log-transformed PK parameter as responding variable. The estimated adjusted mean differences and 90% confidence intervals are exponentiated to provide estimates of the ratio of adjusted geometric means and 90% confidence intervals for the ratios.

Table 14.2.1.1.2
Primary PK Analysis of Natural log-transformed PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last})
Summary of Descriptive Statistics
PK Population

Parameter Statistics	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
C_{max}				
n	xx	xx	xx	xx
Arithmetic Mean	xx.x	xx.x	xx.x	xx.x
Geometric Mean	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx
CV%	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx
$AUC_{0-\infty}$				
n	xx	xx	xx	xx
Arithmetic Mean	xx.x	xx.x	xx.x	xx.x
Geometric Mean	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx
CV%	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx
AUC_{last}				
n	xx	xx	xx	xx
Arithmetic Mean	xx.x	xx.x	xx.x	xx.x
Geometric Mean	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx
CV%	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx

Note: Descriptive statistics are based on natural log-transformed PK parameters.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.2.1.2
Primary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last})
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population

{Programming Note: Repeat Table 14.2.1.1 by using dose-normalized PK Parameters; change footnote accordingly. Add another two columns to the right of the table for Treatment C/B reporting to evaluate dose proportionality. This is the only table in which this calculation is reviewed.}

Table 14.2.1.2.1
Sensitivity Analysis on Primary PK Endpoints: Natural log-transformed, Dose-normalized PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last})
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population

{Programming Note: Repeat Table 14.1.1.1 by using dose-normalized PK Parameters; change footnote accordingly.}

Table 14.2.1.2.2
Primary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (C_{max}, $AUC_{0-\infty}$, and AUC_{last})
Summary of Descriptive Statistics
PK Population

{Programming Note: Repeat Table 14.2.1.2 by using dose-normalized PK Parameters; change footnote accordingly.}

Table 14.2.2.1
Secondary PK Analysis of Natural log-transformed PK Parameters (Partial AUCs)
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population
{Programming Note: Repeat Table 14.2.1.1 by partial AUC Parameters (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, AUC_{12-16}; change footnote accordingly.}

Table 14.2.2.1.1
Sensitivity Analysis on Secondary PK Endpoints: Natural log-transformed PK Parameters (Partial AUCs)
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population
{Programming Note: Repeat Table 14.2.1.1.1 by partial AUC Parameters (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, AUC_{12-16}; change footnote accordingly.}

Table 14.2.2.1.2
Secondary PK Analysis of Natural log-transformed PK Parameters (Partial AUCs)
Summary of Descriptive Statistics
PK Population
{Programming Note: Repeat Table 14.2.1.2 by partial AUC Parameters (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, AUC_{12-16}; change footnote accordingly.}

Table 14.2.2.2
Secondary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (Partial AUCs)
Summary of Estimates of Mean Differences between Treatments and Dose Levels from Mixed Effect Model
PK Population
{Programming Note: Repeat Table 14.2.1.1 by dose-normalized partial AUC Parameters (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, AUC_{12-16}; change footnote accordingly.}

Table 14.2.2.2.1
Sensitivity Analysis on Secondary PK Endpoints: Natural log-transformed, Dose-normalized PK Parameters (Partial AUCs)
Summary of Estimates of Mean Differences between Treatments from Mixed Effect Model
PK Population
{Programming Note: Repeat Table 14.2.1.1.1 by dose-normalized partial AUC Parameters (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, AUC_{12-16}; change footnote accordingly.}

Table 14.2.2.2.2
Secondary PK Analysis of Natural log-transformed, Dose-normalized PK Parameters (Partial AUCs)
Summary of Descriptive Statistics
PK Population
{Programming Note: Repeat Table 14.2.1.2 by dose-normalized partial AUC Parameters (e.g. AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, AUC_{9-12}, AUC_{12-16}; change footnote accordingly.}

Table 14.2.2.3
Secondary PK Analysis of Natural log-transformed PK Parameters (K and $T_{1/2}$)
Summary of Descriptive Statistics
PK Population
{Programming Note: Repeat Table 14.2.1.2 by PK Parameters K, $T_{1/2}$; change footnote accordingly.}

Table 14.2.2.4
Secondary PK Analysis of PK Parameters (t_{max} and t_{lag})
Summary of Descriptive Statistics
PK Population

Parameter Statistics	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
t_{max}				
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx
t_{lag}				
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx

SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.2.2.5
Secondary PK Analysis: Summary of Plasma Concentration of d-MPH (unit)
PK Population

Timepoint Statistics	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
Pre-dose				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx
CV%	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx
0.5 hr Post-dose				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx
CV%	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx
1 hr Post-dose				
…				

{Programming Notes: Continue for all post-dose timepoints for PK collection}

Note: Treatment groups are based on treatment received.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Table 14.3.1.1.1
Summary of all TEAEs
Safety Population

Category	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
All Periods	xx	xx	xx	xx
Subjects with at least one				
Treatment Emergent Adverse Event (TEAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
TEAE Related to Procedure	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event (SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE Related to Procedure	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Study or Drug Withdrawal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

{Programming notes: Repeat for Period 1, 2, 3, 4 respectively}

Note: Percentages are based on the number of subjects treated within the specified period. Adverse events are considered treatment emergent for a period if the event begins at the time of or after drug administration for a specified period; events are reported based on the treatment received during a specified period. Subjects are counted only once within a specified period for each category of reporting. If a particular event is missing severity or relationship, then the maximum severity or strongest relationship will be assumed. Subjects are counted only once for each adverse event category. Medications are displayed alphabetically by ATC and similarly by Preferred Term within ATC.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: Each period must display a denominator. This denominator will represent the number of patients treated in each period.

Table 14.3.1.1.2
Summary of all TEAEs, Non-Current Cigarette Smokers
Safety Population
{Programming Note: Repeat Table 14.3.1.1.1 on subset of non-current cigarette smokers.}

Table 14.3.1.1.3
Summary of all TEAEs, Current Cigarette Smokers
Safety Population
{Programming Note: Repeat Table 14.3.1.1.1 on subset of current cigarette smokers.}

Table 14.3.1.2.1
TEAEs by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
All Periods	xx	xx	xx	xx
Number of subjects with at least one TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…				

{Programming notes: Repeat for Period 1, 2, 3, 4 respectively}

Note: Percentages are based on the number of subjects treated within the specified period. Adverse events are considered treatment emergent for a period if the event begins at the time of or after the drug administration for a specified period; events are reported based on the treatment received during a specified period. Subjects are counted only once within a specified period for each category of reporting (e.g. system organ class [SOC] and preferred term [PT]). If a particular event is missing severity or relationship, then the maximum severity or strongest relationship will be assumed. Events are displayed alphabetically by System Organ Class and similarly by Preferred Term within System Organ Class.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: Each period must display a denominator. This denominator will represent the number of patients treated in each period.

Table 14.3.1.2.2
TEAEs by SOC and Preferred Term, Non-Current Cigarette Smokers
Safety Population
{Programming Note: Repeat Table 14.3.1.2.1 on subset of non-current cigarette smokers.}

Table 14.3.1.2.3
TEAEs by SOC and Preferred Term, Current Cigarette Smokers
Safety Population
{Programming Note: Repeat Table 14.3.1.2.1 on subset of current cigarette smokers.}

Table 14.3.1.3
TEAEs by SOC, Preferred Term and Severity
Safety Population

System Organ Class Preferred Term Severity	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
All Periods	xx	xx	xx	xx
Number of subjects with at least one TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severe				
…				

{Programming notes: Repeat for Period 1, 2, 3, 4 respectively}

Note: Percentages are based on the number of subjects treated within the specified period. Adverse events are considered treatment emergent for a period if the event begins at the time of or after the drug administration for a specified period; events are reported based on the treatment received during a specified period. Subjects are counted only once within a specified period for each category of reporting (e.g. system organ class [SOC] and preferred term [PT]). If a particular event is missing severity, then the maximum severity has been assumed. Events are displayed alphabetically by System Organ Class and similarly by Preferred Term within System Organ Class.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: Each period must display a denominator. This denominator will represent the number of patients treated in each period.

Table 14.3.1.4
TEAEs by SOC, Preferred Term and Relationship to Treatment
Safety Population

System Organ Class Preferred Term Relationship to Treatment	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
All Periods	xx	xx	xx	
Number of subjects with at least one TEAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Procedure Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Known	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Related to Study Drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Procedure Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Known	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…				

{Programming notes: Repeat for Period 1, 2, 3, 4 respectively}

Note: Percentages are based on the number of subjects treated within the specified period. Adverse events are considered treatment emergent for a period if the event begins at the time of or after the drug administration for a specified period; events are reported based on the treatment received during a specified period. Subjects are counted only once within a specified period for each category of reporting (e.g. system organ class [SOC] and preferred term [PT]). If a particular event is missing relationship, then strongest relationship will be assumed. Events are displayed alphabetically by System Organ Class and similarly by Preferred Term within System Organ Class.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: Each period must display a denominator. This denominator will represent the number of patients treated in each period. Also note that this table is the only one in this section (14.1) which needs to add the All CTx-1301 and All Focalin™ columns for reporting.

Table 14.3.1.5
TEAEs leading to Death by SOC and Preferred Term
Safety Population
{Programming Note: Repeat 14.3.1.2 subset to TEAEs leading to death}

Table 14.3.1.6
TESAEs by SOC and Preferred Term
Safety Population
{Programming Note: Repeat 14.3.1.2 subset to TESAEs }

Table 14.3.1.7
AEs leading to Study or Drug Withdrawal by SOC and PT
Safety Population
{Programming Note: Repeat 14.3.1.2 subset to AEs leading to study or drug withdrawal}

Table 14.3.2.1
Summary of Biochemistry by Treatment
Safety Population

Parameter Visit Statistics	Treatment A (N=xx)		Treatment B (N=xx)		Treatment C (N=xx)		Treatment D (N=xx)	
	Absolute Values	Change from Baseline	Absolute Values	Change from Baseline	Absolute Values	Change from Baseline	Absolute Values	Change from Baseline
Analyte 1 (unit)								
Baseline								
n								
Mean								
Standard Deviation								
Median								
Minimum, Maximum								
EOS/ET Visit								
n								
Mean	xx	xx	xx	xx	xx	xx	xx	xx
Standard Deviation	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

{Programming Notes: Repeat for all other parameters}

Note: Baseline is the last observation prior to the first dose of study medication. Data is presented based on the last treatment received prior to the EOS/ET visit.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting. Baseline values will only be reported in the Overall column only.

Table 14.3.2.2
Summary of Hematology by Treatment
Safety Population
{Programming Note: Repeat 14.3.2.1 with hematology analytes}

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting.

Table 14.3.2.3
Summary of Urinalysis by Treatment
Safety Population
{Programming Note: Repeat 14.3.2.1 with urinalysis analytes}

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting.

Table 14.3.2.4
Biochemistry Shift from Baseline to EOS/ET Visit
Safety Population

Treatment prior to EOS/ET Visit Parameter Category	Baseline Category			
	Low	Normal	High	Missing
Treatment A (N=xx)				
Analyte 1 (unit)				
Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

{Programming Note: Continue for all applicable parameters and treatment groups}

Note: Percentages are 100*n/N. Baseline is the last observation prior to the first dose of study medication. Data is presented based on the last treatment received prior to the EOS/ET visit.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ groups added (all 14.3) but also needs Overall reporting.

Table 14.3.2.5
Hematology Shifts from Baseline to EOS/ET Visit
Safety Population
{Programming Note: Repeat 14.3.2.4 with hematology analytes}

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ groups added (all 14.3) but also needs Overall reporting.

Table 14.3.2.6
Urinalysis Shifts from Baseline to EOS/ET Visit
Safety Population
{Programming Note: Repeat 14.3.2.4 with urinalysis analytes}

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ groups added (all 14.3) but also needs Overall reporting.

Table 14.3.3.1
Summary of Physical Examination by Treatment
Safety Population

Body System Visit Category	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
Body System 1				
Baseline				
Normal				
Abnormal, not clinically significant				
Abnormal, clinically significant				
Day 6 Visit	xx	xx	xx	xx
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, not clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
EOS/ET Visit	xx	xx	xx	xx
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, not clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on non-missing assessments at scheduled visit. The baseline value is the last assessment prior to first dose of study medication. Treatment groups are based on the last treatment received prior to assessment. Early termination data will be reported based on the last treatment received prior to discontinuation.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY
Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting. Baseline values will only be reported in the Overall column only.

Table 14.3.4.1
Summary of Vital Signs by Treatment
Safety Population

Parameter Timepoint Statistics	Treatment A (N=xx)		Treatment B (N=xx)		Treatment C (N=xx)		Treatment D (N=xx)	
	Absolute Values	Change from Baseline	Absolute Values	Change from Baseline	Absolute Values	Change from Baseline	Absolute Values	Change from Baseline
Parameter (unit)								
Period 1, Pre-dose								
n	xx		xx		xx		xx	
Mean	xx.x		xx.x		xx.x		xx.x	
Standard Deviation	xx.xx		xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x		xx.x	
Minimum, Maximum	xx, xx		xx, xx		xx, xx		xx, xx	
Period 1, 1 hr Post-dose								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Period 1, 2 hr Post-dose								
…								
EOS/ET Visit								

{Programming Notes: Continue for all post-dose timepoints for vital signs and all parameters, and repeat for Period 1, 2, 3, 4 respectively}

Note: Treatment groups are based on treatment received. Early termination data will be reported based on the last treatment received prior to discontinuation.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting.

Table 14.3.5.1
Summary of ECG Parameters by Treatment
Safety Population
{Programming Notes: Repeat 14.3.4.1 with ECG parameters and timepoints}

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting.

Table 14.3.5.2.1
Incidence of Investigator ECG Interpretation by Treatment
Safety Population

Timepoint Category	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
Period 1, Pre-dose				
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, not clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 1, 6 hr Post-dose				
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, not clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Period 1, 28 hr Post-dose				
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, not clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
….				
EOS/ET Visit				
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, not clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, clinically significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

{Programming notes: Repeat for Period 1, 2, 3, 4 respectively}

Note: Treatment groups are based on treatment received. Early termination data will be reported based on the last treatment received prior to discontinuation.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting.

Table 14.3.5.2.2
Incidence of Investigator ECG Interpretation by Treatment, Non-Current Cigarette Smokers
Safety Population
{Programming Note: Repeat Table 14.3.5.2.1 on subset of non-current cigarette smokers.}

Table 14.3.5.2.3
Incidence of Investigator ECG Interpretation by Treatment, Current Cigarette Smokers
Safety Population
{Programming Note: Repeat Table 14.3.5.2.1 on subset of current cigarette smokers.}

Table 14.3.6.1
C-SSRS, Incidence of Ideation/Behaviour by Treatment
Safety Population

Visit Category	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	Treatment D (N=xx)
Baseline				
Any Suicidal Ideation				
Any Suicidal Behaviour				
Day 3 Visit	xx	xx	xx	xx
Any Suicidal Ideation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Any Suicidal Behaviour	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Day 6 Visit	xx	xx	xx	xx
Any Suicidal Ideation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Any Suicidal Behaviour	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Day 9 Visit	xx	xx	xx	xx
Any Suicidal Ideation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Any Suicidal Behaviour	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

{Programming Notes: Repeat for EOS/ET visit}

Note: Percentages are based on non-missing assessments at scheduled visit. The baseline value is the last assessment prior to first dose of study medication. Treatment groups are based on the last treatment received prior to assessment. Early termination data will be reported based on the last treatment received prior to discontinuation.
SOURCE: Listings xx.x.x, xx.x.x
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This table is one of the selected in this section (14.3) which not only needs to have the All CTx-1301 and All Focalin™ columns added (all 14.3) but also needs an Overall column for reporting. Baseline value will only be reported in the Overall column only.

12.3. Planned Figure Shells

Figure 14.2.2.6.1
Plasma Concentration of d-MPH Scatterplot (linear)
PK Population
{Programming Note: Scatter plot of plasma concentration by subject. Y = plasma concentration (linear scale), X = Time}

Figure 14.2.2.6.2
Plasma Concentration of d-MPH Scatterplot (semi-logarithmic)
PK Population
{Programming Note: Scatter plot of plasma concentration by subject. Y = plasma concentration (semi-logarithmic scale), X = Time}

Figure 14.2.2.6.3
Mean Plasma Concentration of d-MPH vs. Time by Treatment (linear)
PK Population
{Programming Note: Scatter plot of mean plasma concentration by treatment. Y = plasma concentration (linear scale), X = Time}

Figure 14.2.2.6.4
Mean Plasma Concentration of d-MPH vs. Time by Treatment (semi-logarithmic)
PK Population
{Programming Note: Scatter plot of mean plasma concentration by treatment. Y = plasma concentration (semi-logarithmic scale), X = Time}

12.4. Planned Listing Shells

Listing 16.2.1.1
Study Populations and Disposition
All Enrolled Subjects (ITT)

Planned Treatment: Sequence x

Subject ID	Enrolled	Cohort	Actual Treatment Sequence	SAF	PK	Completed Study?	Date of Completion/ Discontinuation	Reason for Discontinuation
XXXXX	Yes	1	Sequence x	Yes	Yes	Yes	DDMMMYYYY	
XXXXX	Yes	1	Sequence x	Yes	Yes	No	DDMMMYYYY	xxxxxxxxxx
XXXXX	Yes	2	Sequence x	Yes	Yes	Yes	DDMMMYYYY	

Note: PK = Pharmacokinetic Population, SAF = Safety Population.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.1.2
Randomization and Treatment Completion
All Enrolled Subjects (ITT)

Planned Treatment: Sequence x

Subject ID	Cohort	Randomization Number	Period (Planned Treatment Day)	Treatment Date (Study Day) [1]	Planned Treatment	Actual Treatment
XXXXX	1	xxxx	1 (Day 0)	DDMMMYYYY (xx)	Treatment A	Treatment A
			2 (Day 3)	DDMMMYYYY (xx)	Treatment D	Treatment D
			3 (Day 6)	DDMMMYYYY (xx)	Treatment B	Treatment B
			4 (Day 9)	DDMMMYYYY (xx)	Treatment C	Treatment C

[1] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.2.1
Inclusion and Exclusion Criteria
All Subjects

Not Randomized

Screening ID/Subject ID	Did subject meet all eligibility criteria?	Criteria Not Met	Reason Not Met
XXXXX	No	Inclusion #1 Exclusion #2	xxxxxxxxxxxxx xxxxxxxxxxxxxxxxxx

{Programming notes: Repeat for Treatment Sequence 1, 2, 3, 4, where "Subject ID" will take place of "Screening ID" in 1st column header.}

XXXXX	Yes		
XXXXX	Yes		

Note: Randomized patients will have both a screening and subject identification number; patients who have not been randomized will be displayed by their screening number only.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.2.2
Protocol Deviations
All Enrolled Subjects (ITT)

Planned Treatment: Sequence x

Subject ID	Event Date	Event Report Date	Event Type	Event Category	Description
XXXXX	DDMMMYYYY	DDMMMYYYY	Major	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
XXXXX	DDMMMYYYY	DDMMMYYYY	Major	xxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxx
XXXXX	DDMMMYYYY	DDMMMYYYY	Minor	xxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

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Listing 16.2.4.1
Demographics
All Enrolled Subjects (ITT)

Planned Treatment: Sequence x

Subject ID	Cohort	Informed Consent Date: Protocol Version	Date of Birth	Age (years)	Gender	If female, childbearing potential?	Ethnicity	Race	Baseline Height (cm)	Baseline Weight (kg)	Baseline BMI (kg/m2)	Cigarettes Smoking Status	Number of Cigarettes Smoked/day	Cigarettes Smoking Start Date/End Date
XXXXX	1	DDMMMYYYY: v1.0	DDMMMYYYY	xx	Female	Yes	xxxxxxxx	xxxxx	xx	xx	xx	Never		
XXXXX	1	DDMMMYYYY: v1.0	DDMMMYYYY	xx	Female	No	xxxxxxx	xxxxx	xx	xx	xx	Former	xx	DDMMMYYYY/ DDMMMYYYY
XXXXX	2	DDMMMYYYY: v3.0	DDMMMYYYY	xx	Male		xxxxxx	xxxx	xx	xx	xx	Current	xx	

T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

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Listing 16.2.4.2
Medical History
Safety Population

Planned Treatment: Sequence x

Subject ID	Any Medical History?	System Organ Class [1]/ Preferred Term/ Verbatim Term	Start Date	End Date/Ongoing
XXXXX	Yes	XXXXXXXXXXXXXXXXXXXXXX/ XXXXXXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY
XXXXX	Yes	XXXXXXXXXXXXXXXXXXXXXX/ XXXXXXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	Ongoing
XXXXX	No			

[1] Medical history was coded using MedDRA version 22.0.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.4.3
Prior and Concomitant Medication
Safety Population

Planned Treatment: Sequence x

Subject ID	Any Meds?	Type [1]	Anatomic Therapeutic Class (level 4) [2]/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ End Date (Study Day) [3]	Indication	Dose (unit)/ Route/ Frequency
XXXXX	Yes	C1, C2, C3	XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ DDMMMYYYY (xx)	xxxxxxxxxx	XXXXXXXXXXXXXXXXXX <units> / XXXXXXX/ XXXXXXXXXXXXXXXXXXXX
		C1, C2, P	XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ ONGOING	xxxxxxx	XXXXXXXXXXXXXXXXXX <units> / XXXXXXX/ XXXXXXXXXXXXXXXXXXXX
XXXXX	No					
XXXXX	Yes	C1, P	XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ ONGOING	xxxxxxx	XXXXXXXXXXXXXXXXXX <units> / XXXXXXX/ XXXXXXXXXXXXXXXXXXXX

[1] C1-C4 = Concomitant medication, any medications continuing or starting during Period 1-4; P = Prior medication, any medications that started prior to the first administration of study medication on Day 0 whether or not they were stopped prior to first administration of study medication; ATC = Anatomic Therapeutic Chemical.
[2] Medications were coded using WHO-DD v. March 1, 2019 and reported in ATC Level 4.
[3] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.4.4
Cigarettes Smoking Log
Safety Population

Planned Treatment: Sequence x

Subject ID	Current Cigarette Smoker?	Visit (Study Day [1])	Any Cigarettes Smoked This Day?	Smoking Start Date	Smoking Start Time
XXXXX	No				
XXXXX	Yes	Clinic Check-in (xx)	Yes	DDMMMYYYY	HH:MM
		Tolerability Test (xx)	Yes	DDMMMYYYY	HH:MM
		Day 0 Assessment (xx)	No		
		Day 1 Non-Assessment (xx)	No		
		…			

[1] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.5.1
Study Drug Administration
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit	Drug Administered ?	Reason not administered	Date of administration (Study Day) [2]	Time of administration	Restriction from fluids [1] completed?	Reason not completed	Were 240 mL of water administered ?	Mouth check performed?	Reason not checked
XXXXX	Day 0	Yes		DDMMMYYYY (xx)	HH:MM	Yes		Yes	Yes	
	Day 3	Yes		DDMMMYYYY (xx)	HH:MM	Yes		Yes	Yes	
	Day 6	Yes		DDMMMYYYY (xx)	HH:MM	Yes		Yes	Yes	
	Day 9	Yes		DDMMMYYYY (xx)	HH:MM	No	xxxxxxxxxxxxx	No	No	xxxxxxxxxx
XXXXX										

[1] Restriction from fluids is completed is the subject complete the 10-hour overnight fast pre-dose and 4-hour post-dose fast as well as the 1-hour pre-dose and 2-hour post dose restriction from fluids.
[2] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.5.2
Tolerability Drug Administration
Safety Population

Planned Treatment: Sequence x

Subject ID	Test drug Administered?	Reason not administered	Date of administration (Study Day) [1]	Time of administration	Test drug safety Tolerated?
XXXXX	Yes		DDMMMYYYY (xx)	HH:MM	Yes
XXXXX	No	xxxxxxxxxxxxxxxxx			

[1] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.6.1
Plasma Concentration of d-MPH
PK Population

Planned Treatment: Sequence x

Subject ID	Visit	PK samples collected?	Reason not collected	Timepoint	Sample collected?	Reason not collected	Date collected	Time collected	Arm used	Plasma concentration (unit)
XXXXX	Day 0	Yes		Pre-dose	Yes		DDMMMYYYY	HH:MM	Right	xx
				0.5 hr Post-dose	Yes		DDMMMYYYY	HH:MM	Right	xx
				1 hr Post-dose	Yes		DDMMMYYYY	HH:MM	Right	xx
				1.5 hr Post-dose	Yes		DDMMMYYYY	HH:MM	Right	xx
				…						
				28 hr Post-dose	Yes		DDMMMYYYY	HH:MM	Right	xx
	Day 3	Yes		Pre-dose	No	xxxxxxxx				
				0.5 hr Post-dose	Yes		DDMMMYYYY	HH:MM	Right	xx
				…						
	Day 6	No	xxxxxxxxx							
	Day 9	…								
	EOS/ET	Yes		N/A	N/A	N/A	DDMMMYYYY	HH:MM	Right	xx

T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

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Listing 16.2.6.2
PK Parameters
PK Population

Planned Treatment: Sequence x

Subject ID	Period (Treatment Day)	Planned Treatment	Actual Treatment	Parameter (Unit)	Value
XXXXX	1 (Day 0)	Treatment A	Treatment A	XXX	xx
				XXXX	xx
				XXXXX	xx
				XXX	xx
				XXXX	xx
				XXX	xx
	2 (Day 3)	Treatment B	Treatment B	XXX	xx
				XXXXX	xxx
				...	
	3 (Day 6)				
	4 (Day 9)				

T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.7.1
All Adverse Events

Planned Treatment: Sequence x

Subject ID [1]	System Organ Class [2]/ Preferred Term/ Verbatim Term	Start Datetime (Study Day) [3]/ End Datetime (Study Day)	Serious	Severity/ Relationship to Study Drug(s)	Outcome/ Med treatment received/ Action taken with Study Drug	CA/DIS/HO/ DE/LT/OTH [4]	TEAE (Period) [5]
XXXXX	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	DDMMMYYYY:HH:MM (xx)/ DDMMMYYYY:HH:MM (xx)	No	xxxxxxx/ xxxxxxxxxxxx	xxxxxxxxxxxxx/ xxxxxxxxxx xxxxxx/ xxxxxxxxxxxxxx	No/No/No/ No/No/No	Yes (1)
XXXXX	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxxxxxx/ xxxxxxxxxx xxxxxxxxxxx	DDMMMYYYY:HH:MM (xx)/ DDMMMYYYY:HH:MM (xx)	Yes	xxxxxxx/ xxxxxxxxxxxx	xxxxxxxxxxxxx/ xxxxxxxxxx/ xxxxxxxx	No/No/Yes/ No/No/Yes	Yes (4)
XXXXX	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	DDMMMYYYY:HH:MM (xx)/ ONGOING	No	xxxxxxx/ xxxxxxxxxxxx	xxxxxxxxxxxxx/ xxxxxxxxxx / xxxxxx	No/No/No/ No/No/No	No (2)

[1] For patients not randomized or treated, (Planned Treatment: Not Treated) this column will list Screening ID.
[2] Adverse Events were coded using MedDRA version 22.0.
[3] Study Day = Assessment Date – Date of First Dose
[4] DE = Death (fatal), LT = Life-threatening event, HO = Hospitalization or prolongation of hospitalization, DIS = Persistent or significant disability/incapacity, CA = Congenital abnormality or birth defect, OTH = Other important medical event.
[5] TEAE is defined as any adverse event with an onset date on or after first dose of first treatment period after randomization. TEAE are identified as treatment emergent based period in which the start of the event occurred; an event is only considered treatment emergent for a period if the dose assigned for the period was administered.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Programming note: This is the only listing of AEs which will include patients who screen fail if applicable. At the end of the listings, include Planned Treatment: Not Treated section for reporting patients by Screening ID. If no AEs are identified for patients not treated or randomized, renumber the footnotes and eliminate references to Not Treated.

Listing 16.2.7.2
Serious Adverse Events
Safety Population
{Programming Note: Repeat 16.2.7.1 with only SAEs. Remove references to Screening ID (renumber footnotes and remove Not Treated from reporting if applicable).}

Listing 16.2.7.3
Adverse Events leading to Discontinuation
Safety Population
{Programming Note: Repeat 16.2.7.1 with only AEs leading to discontinuation. Remove references to Screening ID (renumber footnotes and remove Not Treated from reporting if applicable).}

Listing 16.2.7.4
Listing of Deaths
Safety Population
{Programming Note: Repeat 16.2.7.1 with only fatal AEs. Remove references to Screening ID (renumber footnotes and remove Not Treated from reporting if applicable).}

Listing 16.2.8.1
Biochemistry
Safety Population

Planned Treatment: Sequence x

Subject ID /Age/Gender	Analyte (unit)	Visit (Study Day [1])	Sample collected?	Reason not collected	Date collected	Time collected	Test Result [2]	Units	Standard Reference Range Low	Standard Reference Range High	Change from Baseline
XXXXX/xx/M	xxxx (xx)	Screening (xx)	Yes		DDMMMYYYY	HH:MM	xx	xxxx	xx	xx	xx
		Clinic Check-in (xx)	Yes		DDMMMYYYY	HH:MM	xx	xxxx	xx	xx	xx
		Unscheduled (xx)	Yes		DDMMMYYYY	HH:MM	xx	xxxx	xx	xx	xx
		…									
		EOS/ET (xx)	Yes		DDMMMYYYY	HH:MM	xx	xxxx	xx	xx	xx
XXXXX/xx/F	xxxx (xx)										

[1] Study Day = Assessment Date – Date of First Dose
[2] L = low result, H = high result, ^ = abnormal result.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.8.2
Hematology
Safety Population
{Programming Note: Repeat 16.2.8.1 with hematology analytes}

Listing 16.2.8.3
Urinalysis
Safety Population
{Programming Note: Repeat 16.2.8.1 with urinalysis analytes}

Listing 16.2.8.4
Thyroid
Safety Population
{Programming Note: Repeat 16.2.8.1 with TSH}

Listing 16.2.8.5
Urine Drug Screen
Safety Population

Planned Treatment: Sequence x

Subject ID	Analyte	Visit (Study Day [1])	Drug screen performed?	Reason not performed	Date collected	Time collected	Test Result	Comments
XXXXX	xxxxxxx	Screening (xx)	Yes		DDMMMYYYY	HH:MM	Negative	
		Clinic Check-in (xx)	Yes		DDMMMYYYY	HH:MM	Negative	
	xxxxxxx							

[1] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.8.6
Serology
Safety Population
{Programming Note: Repeat 16.2.8.5 with Serology analytes}

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Listing 16.2.8.7
Pregnancy
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit (Study Day [1])	Sample collected?	Reason not collected	Date collected	Time collected	Test Result
XXXXX	Screening (xx)	Yes		DDMMMYYYY	HH:MM	Negative
		No	xxxxxxxxxxx			
	Clinic Check-in (xx)	Yes		DDMMMYYYY	HH:MM	Negative
		Yes		DDMMMYYYY	HH:MM	Negative
	EOS/ET (xx)	Yes		DDMMMYYYY	HH:MM	Negative
XXXXX						

Note: Serum and Urine pregnancy tests are analyzed in women of child-bearing potential only.
[1] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.8.8
Breath Alcohol Test
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit (Study Day [1])	Test performed?	Reason not performed	Date performed	Time performed	Test Result
XXXXX	Screening (xx)	Yes		DDMMMYYYY	HH:MM	Negative
	Clinic Check-in (xx)	No	xxxxxxxxxxx			
XXXXX						

[1] Study Day = Assessment Date – Date of First Dose
[2] L = low result, H = high result, ^ = abnormal result.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.9.1
Physical Examination
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit (Study Day [1])	Exam performed?	Reason not performed	Exam Date	Body System	Result	Abnormal Findings	Clinically Significant [2]
XXXXX	Screening (xx)	Yes		DDMMMYYYY	xxxxxxxxxxxx	xxxxx		
					xxxxxxxxxxxx	xxxxx		
					xxxxxxxxxxxx	xxxxx	xxxxxxxxxx	NCS
					xxxxxxxxxxxx	xxxxx		
					xxxxxxxxxxxx	xxxxx		
					xxxxxxxxxxxx	xxxxx	xxxxxxxxxx	CS
	Clinic Check-in (xx)	No	xxxxxxxxxxx					
	Day 6 (xx)	…						
	EOS/ET (xx)	…						
XXXXX								

[1] Study Day = Assessment Date – Date of First Dose
[2] CS = clinically significant, NCS = not clinically significant
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

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Listing 16.2.9.2
Vital Signs
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit (Study Day [1])	Timepoint	Vital signs assessed?	Reason not assessed	Date Collected	Time Collected	Heart Rate (bpm)	SBP/DBP [2] (mmHg)	Arm used for SBP/DBP	Weight (kg)	Height (cm)	BMI (kg/m2)
XXXXX	Screening (xx)		Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right	xx	xx	xx
	Clinic Check-in (xx)		Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right	xx		
	Tolerability Test (xx)		Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right			
	Day 0 (xx)	Pre-dose	Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right			
		1 hr Post-dose	Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right			
		2 hr Post-dose	Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right			
		6 hr Post-dose	Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right			
		28 hr Post-dose	Yes		DDMMMYYYY	HH:MM	xx	xx/xx	Right			
	Day 3 (xx)	…										
	…											
	EOS/ET (xx)											
XXXXX												

[1] Study Day = Assessment Date – Date of First Dose
[2] SBP = Systolic blood pressure; DBP = Diastolic blood pressure
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

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Listing 16.2.9.3
Electrocardiogram (ECG)
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit (Study Day[1])	Timepoint	ECG assessed?	Reason not assessed	ECG Date	ECG Time	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcF (msec)	VR [2] (msec)	Rhythm	Investigator Interpretation	Comments
XXXXX	Screening (xx)		Yes		DDMMMYYYY	HH:MM	xx	xx	xx	xx	xx	xx	Normal	xx	xxxxxxxx
	Clinic Check-in (xx)		Yes		DDMMMYYYY	HH:MM	xx	xx	xx	xx	xx	xx	Normal	xxxxxxxxxx	xxxxxxx
	Tolerability Test (xx)		Yes		DDMMMYYYY	HH:MM	xx	xx	xx	xx	xx	xx	Normal		
	Day 0 (xx)	Pre-dose	Yes		DDMMMYYYY	HH:MM	xx	xx	xx	xx	xx	xx	Normal		
		6 hr Post-dose	Yes		DDMMMYYYY	HH:MM	xx	xx	xx	xx	xx	xx	Normal		
		28 hr Post-dose	Yes		DDMMMYYYY	HH:MM	xx	xx	xx	xx	xx	xx	Normal		
	Day 3 (xx)	…													
	…														
	EOS/ET (xx)														
XXXXX															

[1] Study Day = Assessment Date – Date of First Dose
[2] VR = Ventricular Rate.
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

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Listing 16.2.9.4
C-SSRS
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit (Study Day [1])	Completed?	Reason not completed	Assessment Date	Category	Question Text	Result
XXXXX	Screening (xx)	Yes		DDMMMYYYY	Suicidal Ideation	xxxxxxxxxxxx xxxxx xxxxxxxxx	xxxxxxx
						xxxxxxxxx xxxxx xxxxxx	xxxxx
						xxxxxxxxxx xxxxx xxxxxxxxx	xxxxxx
					Intensity of Ideation	xxxxxxxxxxxx xxxxx xxxxxxxxx	xxxxxxx
						xxxxxxxxx	xxxxx
						xxxxxxxxxx xxxxxxxxx	xxxxxxx
					Suicidal Behaviour	xxxxxxxxxx	xxx
	xxxx (xx)						

Note: C-SSRS = Columbia Suicide Severity Rating Scale
[1] Study Day = Assessment Date – Date of First Dose
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Listing 16.2.9.5
M.I.N.I.
Safety Population

Planned Treatment: Sequence x

Subject ID	Visit	Completed?	Reason not completed	Interview Date Start/Stop Time	Module	Question Text	Result
XXXXX	Screening	Yes		DDMMMYYYY HH:MM/HH:MM	A	xxxxxxxxxxxx xxxxx xxxxxxxxx	xxxxxxx
						xxxxxxxxx xxxxx xxxxxx	xxxxx
						xxxxxxxxxx xxxxx xxxxxxxxx	xxxxxx
					B	xxxxxxxxxxxx xxxxx xxxxxxxxx	xxxxxxx
						xxxxxxxxx	xxxxx
						xxxxxxxxxx xxxxxxxxx	xxxxxxx
XXXXX							

Note: M.I.N.I. = MINI International Neuropsychiatric Interview
T:\Cingulate\CTx-1301\...\xxxxxx.sas run on DDMMMYYYY at HH:MM on data extracted on DDMMMYYYY

Appendix 1: List of Abbreviations

Abbreviation	Definition
ADHD	attention deficit and hyperactivity disorder
AE	adverse event
BLQ	beneath limit of quantification
BMI	body mass index
CI	confidence intervals
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
DBP	diastolic blood pressure
d-MPH	dexmethylphenidate
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European medicines agency
EOS	end of Study
ET	early termination
EU	European Union
FDA	food and drug administration
HR	heart rate

Abbreviation	Definition
ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
ITT	intent-to-treat
MedDRA	medical dictionary for regulatory activities
N	number
NA	not applicable
NCS	non-clinically significant
PD	protocol deviation
PE	physical examination
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TOST	two one-sided hypothesis tests
WHO-DD	world health organization drug dictionary