Clinical Protocol Number: 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.

NCT04138498

16Jan2020

CLINICAL STUDY PROTOCOL

A RANDOMIZED, SINGLE-DOSE, FOUR-SEQUENCE, FOUR-PERIOD, IN-CLINIC CROSS-OVER STUDY IN ADULT ADHD SUBJECTS TO ESTABLISH SAFETY, TOLERABILITY, AND COMPARATIVE BIOAVAILABLITY OF CTx-1301 (DEXMETHYLPHENIDATE) TO THE LISTED DRUG (FOCALIN XR™) UNDER FASTED CONDITIONS

Study Number: CTx-1301-001

Drug Development Phase:	Phase 1
Investigational Product:	Dexmethylphenidate
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Cingulate Therapeutics 1901 W. 47th Place, Suite 310 Kansas City, KS 66205
Principal Investigator	Debra Kelsh, MD
Date:	Version 4.0 16 January 2020

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

SUMMARY INFORMATION

Title:	A 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.
Protocol Number:	CTx-1301-001
Sponsor:	Cingulate Therapeutics
Primary Sponsor contact:	Holly Mitzel Cingulate Therapeutics 1901 W. 47th Place, Suite 310 Kansas City, KS 66205 E: Hmitzel@cingulatetherapeutics.com P: 913-942-2304
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SPONSOR PROTOCOL APPROVAL

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.
Protocol Number:	CTx-1301-001
Protocol Version:	4.0
Date of Version:	16 January 2020
Signed for approval by:	

Dr. Matt Brams, MD
Chief Medical Officer
Cingulate Therapeutics

Dr. Raul Silva, MD
Chief Science Officer
Cingulate Therapeutics

PROTOCOL SIGNATURE PAGE

I have read and understand the contents of this clinical protocol for Study No. CTx-1301-001 date 16 January 2020 and agree to meet all obligations of Cingulate Therapeutics as detailed in all applicable regulations and guidelines.

Signed By:

Principal Investigator
Altasciences Clinical Kansas, Inc.

Date of Signature

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Table 1: Study Synopsis

STUDY SYNOPSIS

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.
Short Title/Acronym	CTx-1301 Comparative BA Study
Protocol Number	CTx-1301-001
Objective(s)	**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 • To evaluate dose proportionality of CTx-1301 by evaluating the 6.25 mg dose to the 50 mg dose **Secondary objectives:** • To characterize the pharmacokinetics of dexmethylphenidate (d-MPH) blood plasma levels after dosing • To evaluate safety measurements including ECG, vital signs, lab assessments, physical exam, and occurrence of treatment-emergent adverse events (TEAEs)
Study Design and Methodology	A single-center, randomized, four-sequence, four-period, in-clinic, crossover study in a fasted state. Subjects will be enrolled in approximately 4-5 cohorts (each cohort will enroll approximately 6-12 subjects/cohort) to allow for a recruitment total of approximately 36 completers and at least 32 evaluable subjects.
Number of Subjects	The study will enroll approximately 36 adult ADHD subjects
Diagnosis and Main Inclusion Criteria	Adult subjects aged 18 to 55 years, inclusive, free from any significant diseases/disorders (e.g. psychiatric (excluding ADHD), cardiac, hepatic, renal, and gastrointestinal), and can demonstrate tolerability of a single dose of 40 mg d-MPH will be entered into the study.
Study Product and Planned Use	The investigational product, CTx-1301, is a (Precision Timed Release™ (PTR™) trimodal release d-MPH tablet using an erosion-barrier layer (EBL) technology. The investigational doses of CTx-1301 in this study are 6.25 mg and 50 mg (d-MPH). Tablets will be taken orally with 240 mL of room temperature water. All tablets will be administered under fasted conditions.

Reference therapy	The comparator product (Listed Drug (RLD)) used in this study is Focalin XR™ 5 mg and Focalin XR™ 40 mg (d-MPH). Capsules will be taken orally with 240 mL room temperature water. All capsules will be administered under fasted conditions.
Treatments	Four treatments a. (1) Focalin XR 5mg b. (1) CTx-1301 trimodal dMPH 6.25mg c. (1) Focalin XR 40mg d. (1) CTx-1301 trimodal dMPH 50mg
Study Duration	Each subject's involvement in the study will be 15 days in-clinic (excluding screening). Completion of the clinical study will be defined as last subject, last visit (LSLV) at End of Study (EOS) visit.
Treatment Duration	Subjects will check in on Day -4, receive a test dose for tolerability (40 mg Focalin XR) on Day -3, and if eligible, will be randomized to the study. The study treatment will be administered according to the randomization schedule at Day 0, Day 3, Day 6, and Day 9; subjects will remain in clinic throughout the study. End of study/last visit is the EOS visit. Dosing will be separated by 72 hours (3 days) to allow washout of study drug and reference drug (d-MPH).
PK Sampling Times	Pre-dose (0) and Hours 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 24, and 28.

Criteria for Evaluation	
Pharmacokinetics	The pharmacokinetic parameters to be determined are: Maximum Concentration (C_{max}), Time of Maximum Concentration (T_{max}), terminal elimination constant (K), lag time (T_{lag}), Half Life ($T_{1/2}$), Area Under the Curve from time 0 to 28 hrs (AUC_{last}), Area Under the Curve from time 0 to infinity ($AUC_{0-\infty}$), and partial areas AUC_{0-3}, AUC_{3-6}, AUC_{6-9}, and AUC_{9-12}, and AUC_{12-16}. Additional measures may be evaluated if deemed necessary.
Bioanalytical Method	Analysis of d-MPH in plasma will utilize a validated, high-performance liquid chromatography (HPLC) method using tandaem mass spectrometry (MS/MS) detection for the determination of methylphenidate in human plasma.
Safety	All adverse events (AEs) will be listed for each subject and summarized by the body system and preferred term assigned to the event using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Any serious adverse events (SAEs) will be listed separately.
Statistical Methods	Statistics will be computed and reported for pharmacokinetic and safety parameters obtained. Statistical Analysis Plan (SAP) will be completed a priori and before unblinding and analysis of PK samples.

ABBREVIATIONS

ADHD	Attention Deficit and Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
$AUC_{0\text{-}inf}$	Area Under the Curve from time 0 to infinity
AUC_{last}	Area Under the Curve from time 0 to 28 hrs
BMI	Body Mass Index
C_{max}	Maximum Concentration
CNS	Central Nervous System
eCRF	Electronic Case Report Form
CS	Clinically Significant
C-SSRS	Columbia Suicide Severity Rating Scale
CTx	Cingulate Therapeutics
d-MPH	Dexmethylphenidate
ECG	Electrocardiogram
ENT	Ears, Nose, Throat
EOS	End Of Study
ET	Early Termination
FDA	Food and Drug Administration
FPFV	First Subject First Visit
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GRAS	Generally Regarded As Safe
Hb	Hemoglobin
Hct	Hematocrit
HPLC	High-performance liquid chromatography
Hr.	Hour(s)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
K	Terminal elimination constant
kg	Kilograms
kg/m_2	kilograms Per Meter Squared
L	Liter
LSLV	Last Subject Last Visit
m	Meter
MCH	Mean Cell Hemoglobin
MCV	Mean Cell Volume
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram(s)
min	Minute
mL	Milliliter(s)
mmHg	Millimeters Of Mercury
D-MPH	Dexmethylphenidate
MPH	Racemic Methylphenidate (d, l-MPH)
ms	Millisecond
MS/MS	Tandem mass spetcrometry
mSv	Millisieverts
NCS	Not Clinically Significant
NMS	Neuroleptic Malignant Syndrome
PCP	Primary Care Physician
PK	Pharmacokinetic
RBC	Red Blood Cell
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

TEAE	Treatment Emergent Adverse Event
$T_{1/2}$	Half Life
T_{lag}	Lag time
T_{max}	Time of Maximum Concentration
U	Unit
USV	Unscheduled Visit
WBC	White Blood Cell

Table 2: Study Schedule

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 or ET_{II}	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]	

Table 2: Study Schedule

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 or ET[ll]	Unscheduled (USV)[m]
Urine Screen for Drugs of Abuse	✓	✓							
Breath Alcohol Test	✓	✓							
AE Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
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 by approximately 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 women of child-bearing potential at Screening, Check-In (Day -4), and EOS/ET.
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 by approximately 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.

Table 3: Schedule for Check-In and Tolerability (Day -4 to Day -3)

Time Relative to Dose (hr.)	Subject Activity	Fluid/Food intake [d]	ECG[c]	Vital signs[e]	Safety and AE Monitoring
-12 to -10 (check-in, Day -4)	Assessment of eligibility. Urine analysis for drugs and breath alcohol test [a]	Fasting from at least 10 hr. prior to dosing. Water *ad libitum*			Clinical Safety Labs for Inclusion/Exclusion
-1.00 – 0 (pre-dose)		Decaffeinated Fluids/Water is restricted at least 1 hr. prior to dosing.	ECG should be taken within 60-minute window prior to dosing[c]	✓	
-.50 - 0 (pre-dose)					
0	Dosing	240 mL water w/dose			Continuous AE monitoring
↕	Subject to remain seated[b]	Decaffeinated Fluids/Water is restricted until at least 2 hrs after dosing.		✓	
2				✓	
↕		Fasting from dosing to at least 4 hrs after dosing Water *ad libitum*.			
4		Lunch[d]			
↕		Water *ad libitum*			
6		Snack[d]	ECG[c]	✓	
↕		Water *ad libitum*			
8					
9		Dinner[d]			

Table 3: Schedule for Check-In and Tolerability (Day -4 to Day -3)

Time Relative to Dose (hr.)	Subject Activity	Fluid/Food intake [d]	ECG[c]	Vital signs[e]	Safety and AE Monitoring
↕		Decaffeinated fluid *ad libitum*			
12		Snack[d]			
↕		Decaffeinated Water / decaffeinated fluid *ad libitum*			
14					
↕					
16					
23					
24		Breakfast[d]			
↕					
28			ECG[c]	✓	

[a] Urine analysis for drugs and breath alcohol test will be conducted and reviewed prior to subject dosing. Tests may be repeated at an Investigator's discretion.
[b] Subject must remain seated upright for at least 2 hrs after dosing, unless the subject is required to be supine for a study procedure or experiences an AE. Brief periods of standing are okay under supervision (e.g., to use the restroom). Subjects may be ambulatory or seated upright from hours 2- 4. Activity beyond hour 4 is not restricted with the exception that it shouldn't include any activity that may increase the subject's heart rate.
[c] An ECG should be taken approximately within 60 minutes prior to dosing, hr. 6, and hr. 28 (± 30 min of the target time for post-dose ECGs)
[d] Acceptable water, snack, and lunch/dinner times will be considered ± 30 min of the target time, except for hr 4; hr 4 must occur at hr 4 or +30 min.
[e] Vital signs will be taken within approximately 60 minutes prior to dosing and at 1 hr., 2 hr., 6 hr., and 28 hr. post-dose (+/- 10 minutes).

Table 4: Schedule for Assessment Days Day 0, Day 3, Day 6, and Day 9 Days

Time Relative to Dose (hr.)	Subject Activity	Blood Sampling [b]	Fluid/Food intake[d]	ECG	Vital signs[e]	AE Monitoring
-12 to -10 (pre-dose)	Snack is available if needed		Water *ad libitum*			Continuous AE monitoring (subjects will not be woken to answer question if sleeping)
-10 (pre-dose)			Fasting from at least 10 hr. prior to dosing. Water *ad libitum*			
-1.0 to 0 (pre-dose)		Venipuncture or Insertion of cannula and pre-dose sample.	Decaffeinated Fluids/Water is restricted at least 1 hr. prior to dosing.	ECG should be taken within 60-minute window prior to dosing[c]	Vital signs should be taken within 60-minute window prior to dosing	
-.50 to 0 (pre-dose)						
0	Dosing		240 mL water w/dose			
↕	Subject to remain seated[a]	Blood sampling times: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20 and 24, and 28 hr. post-dose. [b]	Decaffeinated Fluids/Water is restricted until at least 2 hrs after dosing.		✓	
2					✓	
↕			Water *ad libitum* Fasting from dosing to at least 4 hrs after dosing.			
4			Lunch[d]			
↕			Water *ad libitum*			

Table 4: Schedule for Assessment Days Day 0, Day 3, Day 6, and Day 9 Days

Time Relative to Dose (hr.)	Subject Activity	Blood Sampling [b]	Fluid/Food intake[d]	ECG	Vital signs[e]	AE Monitoring
6			Snack[d]	ECG[c]	✓	
↕			Water *ad libitum*			
8						
9			Dinner[d]			
↕			Decaffeinated fluid *ad libitum*			
12			Snack[d]			
↕			Water / decaffeinated fluid *ad libitum*			
14						
↕						
16						
↕						
23						
24			Breakfast[d]			
↕						
28[b]				ECG[c]	✓	
End of Assessment Day	Depart Site [f]					

[a] Subject must remain seated upright for at least 2 hrs. after dosing, unless the subject is required to be supine for a study procedure or experiences an AE. Brief periods of standing are okay under supervision (e.g., to use the restroom). Subjects may be ambulatory or seated upright from hours 2-4. Activity beyond hr. 4 is not restricted with the exception that it shouldn't include any activity that may increase the subject's heart rate.

[b] An acceptable pre-dose PK blood sampling time will be considered -1 to 0 hr of target time (0). Post-dose PK blood sampling time will be considered ± 5 min of the target time; Exact time of PK draw must be recorded to the hr. and minute.

[c] An ECG should be taken approximately within 60 minutes prior to dosing, hr. 6, and hr. 28 (± 30 min of the target time for post-dose ECGs)

[d] Acceptable water, snack, and lunch/dinner times will be considered ± 30 min of the target time, except for hr 4; hr 4 must occur at hr 4 or +30 min.

[e] Vital signs will be taken within approximately 60 minutes prior to dosing and at 1 hr., 2 hr., 6 hr., and 28 hr. post-dose (+/- 10 minutes) Days 0-9. Vital signs on non-dosing days should follow the same schedule as dosing days.

[f] Subject departs site after hr. 28 on EOS/ET day.

INTRODUCTION

Attention-deficit and hyperactivity disorder (ADHD) is the most prevalent psychiatric condition in children. It affects approximately 5-10% of school-aged children.[1,2,3] The hallmark set of symptoms of ADHD include inattention, hyperactivity and impulsivity. Although ADHD was at one time considered a childhood illness that resolved in adolescence, it is now believed that impulsivity and hyperactivity may morph into executive dysfunction and emotional dyscontrol in adults.[4]

Stimulants have been considered the mainstay of pharmacological treatment of ADHD for over seventy years. Their effect on disruptive behavior was discovered in 1937, when these drugs proved to increase compliance, improve academic performance, and reduce motor activity in hyperactive children.[5] Methylphenidate (MPH) is the most frequently prescribed among stimulant agents. It has proven efficacy on ADHD symptoms.[6,7]

Prior to the introduction of the enantiopure d-MPH (d-threo-(R,R)-MPH, dexmethylphenidate,) in 2002, all clinically used MPH formulations contained a racemic (1:1) mixture of d-threo-(R,R)-MPH and l-threo-(R,R)-MPH isomers. The development of d-MPH product was based on the findings that similar improvement on sustained attention was achieved after treatment with d-equivalent doses of d-MPH and d,l-MPH, but not after l-MPH.[8] Clinical efficacy was highly correlated with plasma concentrations of d-MPH. The elimination of the l-isomer does not diminish the efficacy of an acute dose of methylphenidate.[9] The efficacy of the d-isomer was equivalent to the racemic preparation in ameliorating the target symptoms of ADHD and increasing academic productivity. Thus, it was thought that the efficacy of MPH resides in the d-isomer.[8,10,11,12] The short acting form of d-MPH was released to the market[13] and demonstrated clinical efficacy lasting slightly over 5 hrs in open label studies.[14]

To alleviate the need for a mid-day dose (thereby eliminating problems related to dispensing the medication at school), a long-acting formulation of d-MPH was developed that could be administered once a day.[15] Using analogue laboratory classroom studies, the onset of action for this formulation was documented at 30 minutes after medication administration and the duration of affect when compared to placebo demonstrated clinically and statistical differences at 12 hrs after initial administration.[16,17] Despite this, ratings at hour 12 for key symptoms of ADHD yielded results that were worse than baseline symptom levels.

A major drawback to most long acting stimulant products currently on the market is that they do not remain effective more than 12 hours after administration. For many adults and college students this duration in coverage is not sufficiently long. Furthermore, as blood levels drop precipitously during the latter portions of the day, subjects also experience a crash or rebound effect, which often manifests in adverse effects such as irritability, mood changes and worsening of clinical presentations.

The current project is a randomized, single-dose, four-sequence, four-period study in adult ADHD subjects to establish safety and comparative bioavailability of CTx-1301 to the listed drug, Focalin™ XR Extended-Release Capsules.

As shown in Figure 1, the release times of the CTx-1301 trimodal tablet is expected to be:

1) 1st dose, immediate release (35% of the total daily dose)
2) 2nd dose, delayed, sustained release 90 minutes after a 3-4 hour delay (45% of the total daily dose)
3) 3rd dose, delayed, immediate release 7-8 hours post-dose (20% of the total daily dose)

FIGURE 1

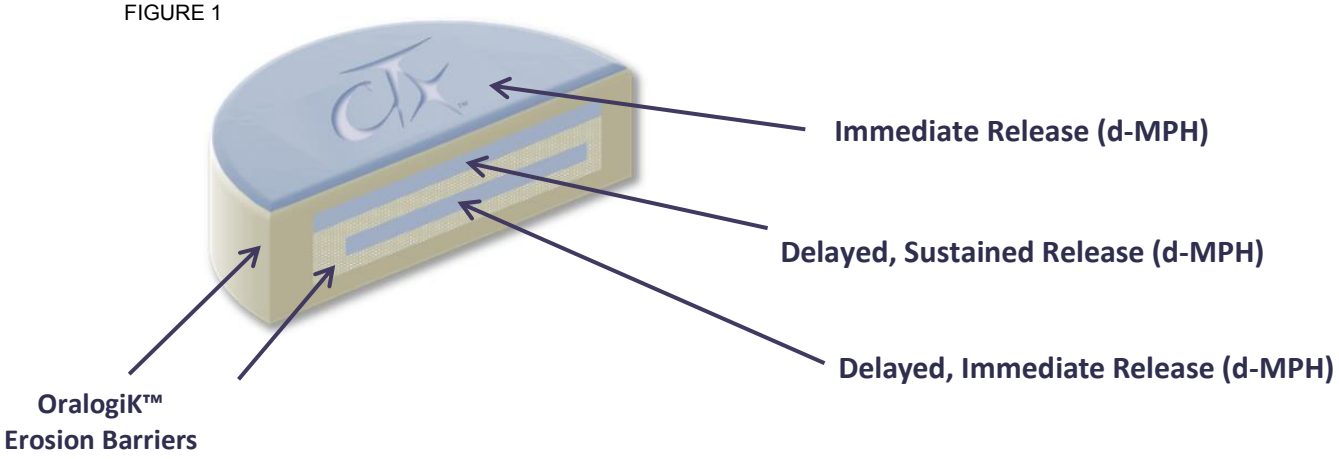

Figure 1: Schematic for Proposed Trimodal CTx-1301 Tablet

The study will comprise of a randomized, single-dose, four-sequence, four-period, in-clinic crossover study in approximately 36 adult ADHD subjects. All subjects considered eligible at Screening will proceed to tolerability test day, dosing 40 mg Focalin XR to evaluate safety and tolerability of the higher dose of d-MPH. If subject is able to safely tolerate the test dose, and meets all inclusion/exclusion criteria, they will be considered eligible for randomization into the study. All subjects will be randomized to receive four treatments throughout the course of the study; one CTx-1301 trimodal d-MPH tablet containing 6.25 mg d-MPH, one Focalin 5 mg XR capsule, one CTx-1301 50 mg tablet, and one 40 mg Focalin XR capsule. Administration of study drug will occur only on Assessment Days; no study drug will be administered during screening or unscheduled days (USVs).

The lowest and highest doses of CTx-1301 (dexmethylphenidate, 6.25 and 50 mg) were selected to bridge to the lowest and highest doses of Focalin XR (dexmethylphenidate, 5 and 40 mg) in this comparative BA study.

1 OBJECTIVES

1.1 PRIMARY OBJECTIVE(S)

- 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

1.2 SECONDARY OBJECTIVE(S)

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

1.3 EXPLORATORY OBJECTIVE(S)

- 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 ENDPOINTS

2.1 PRIMARY ENDPOINT(S)

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

2.2 SECONDARY ENDPOINT(S)

- PK plasma concentrations of d-MPH and PK parameters including partial AUCs (e.g. $AUC_{0\text{-}3}$, $AUC_{3\text{-}6}$, $AUC_{6\text{-}9}$, $AUC_{9\text{-}12}$, and $AUC_{12\text{-}16}$) to examine potential differences between treatments (CTx-1301 6.25 mg vs. FocalinTM XR 5 mg and CTx-1301 50 mg vs. Focalin™ XR 40 mg) within selected time intervals.
- PK plasma concentrations of d-MPH and 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)

2.3 EXPLORATORY ENDPOINT(S)

- 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.

3 INVESTIGATIONAL PLAN

3.1 STUDY 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 subjects, 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 hrs prior to check in on Day -4. Subjects will remain in clinic from Day -4 to the EOS visit.

Subjects which 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). 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. Subjects that early terminate should follow the assessment structure of the EOS day; a final PK draw should be collected and labeled at ET time. Additional unscheduled days 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 5: 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 4x4 Williams design. Williams Design is a special case of Latin square design and is balanced for carryover effects.

Table 6: 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 hours prior to hr. 0 on Day -3). Subjects may receive a snack (if needed) from hours -12 to -10 on Day -4; at -10 hrs, all subjects must fast until at least hr. 4 post-dose. Water is restricted at least 1 hour prior to dosing and at least 2 hours 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 hours 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 hr. post-dose (see Table 4). Vital signs (blood pressure and pulse) and ECG will be taken at the protocol-specified time points until 28 hr. 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 RATIONALE FOR STUDY DESIGN

This study will use pharmacokinetic (pk) analysis to investigate the *in vivo* behavior of CTx-1301 tablets compared to Focalin XR™ (RLD) for bridging to the RLD.

The randomized crossover study design allows subjects to act as their own control, thereby optimizing model sensitivity by reducing the risk of subject variability between the test formulation and comparator.

The three-day period (72 hrs) between Assessment Days is sufficient for the washout of the drug (the plasma elimination half-life of d-MPH is approximately 3 hrs.). Subjects are kept in-clinic to increase compliance and reduce drop-out rates.

ADHD subjects meeting all inclusion criteria and no exclusion criteria will be recruited for the study.

4 STUDY POPULATION

4.1 SOURCE AND NUMBER OF SUBJECTS

The study site will recruit potential subjects from its database, referral network, as well as local advertising, if required.

Approximately 36 subjects will be randomized in the study to achieve completion of approximately 32 evaluable subjects for the full study (approximately 8 in each sequence).

4.2 CRITERIA FOR EVALUATION

Eligibility of subjects for study enrollment will be based on the results of a screening medical history, physical examination, mental state examination, vital signs (blood pressure and pulse), breath alcohol, urine drugs of abuse, tolerance of 40 mg Focalin XR on the test day, and clinical laboratory tests. All screening tests will be performed and assessed by qualified study personnel. The nature of any conditions present at the time of the physical and mental state examinations and any pre-existing conditions will be documented and carefully evaluated by an Investigator.

4.3 INCLUSION CRITERIA

1. **Gender**
    a. Male or Female

2. **Age**
    a. Aged between 18 and 55 years inclusive.

3. **Weight and BMI**
    a. Body weight ≥ 50 kg
    b. BMI ≥ 18 and ≤ 35

4. **Compliance**
    a. Understands and is willing, able and likely to comply with all study procedures and restrictions.
    b. If sexually active, male subjects must use the double-barrier method (condom and spermicide) for birth control during the study and for 90 days following the last administration of study drug.
    c. If sexually active, female subjects of child-bearing potential must use an acceptable method of contraception, including abstinence from heterosexual intercourse, hormonal contraceptives, intrauterine device (IUD) with or without hormones, or double-barrier method (e.g. condom and spermicide), during the study and for 30 days following the last administration of study drug.
    d. Male subjects must agree not to donate sperm during the study and for 90 days following the last administration of study drug.
    e. Female subjects must agree not to donate eggs during the study and for 30 days following the last administration of study drug.

5. **Consent**
    a. Demonstrates understanding of the study and willingness to participate as evidenced by voluntary written informed consent (signed and dated) obtained before any study-related activities are performed.

6. **Indication**
    a. Subject must report history of diagnosis of ADHD.

b. If subject is currently taking stimulant medication, they must be willing and able to safely abstain from any other ADHD treatment during 96 hrs. prior to check-in on Day -4 and through the complete duration of the study.

7. General Health

a. Good general health (in the opinion of an investigator) with no clinically significant or relevant abnormalities on medical history or physical examination which could affect the safety of the subject or study data.
b. No vomiting or fever within 24-hours of check-in at Day -4

c. Subject has sufficient venous access to allow cannulation and/or venipuncture to obtain the required volume of blood for this study.

d. Subject must currently be taking or previously have taken a stimulant medication for ADHD.

8. Smoking/Caffeine/Alcohol

a. Subject must be able to refrain from smoking cigarettes 1 hour prior to dosing and 7 hours after dosing on dosing days. Subject must agree not to smoke more than one cigarette per hour, not to exceed 10 cigarettes per day.
b. Subject must be able to refrain from caffeine for 10 hours prior to check-in at Day -4 and for the duration of the study.
c. Subject must be able to refrain from using alcohol 48 hrs. prior to Day -4 and for the duration of the study.

9. ADHD Medication History

a. Subject's medication history suggests they will be able to tolerate a 40 mg dose of dexmethylphenidate.
b. Subject must demonstrate tolerability of dexmethylphenidate assessed by tolerability day/test dose of 40 mg Focalin XR as evaluated by the investigator.

4.4 EXCLUSION CRITERIA

1. Medical History

a. Current and/or recurrent disease or illness that, in the opinion of an investigator, could affect the study conduct, study outcome, subject safety, or pharmacokinetic (PK) assessments (e.g., hepatic disorders, renal insufficiency, non-self-limiting gastrointestinal disorders, congestive heart failure).

b. Current and/or previous history of any other serious, severe or unstable psychiatric illness which in the opinion of the investigator, may require treatment (e.g. anxiety, psychosis, mood disorder, motor tics or suicidality) or make the subject unlikely to fully complete the study, and/or any condition that presents undue risk from the study medication or procedures.

c. Subject cannot have suicidal thoughts within the last 6 months as supported by the Columbia Suicide Severity Rating Scale (C-SSRS).

d. Positive test results for Human Immunodeficiency Virus (HIV)-1/HIV-2 antibodies, Hepatitis B surface antigen (HBsAg) or Hepatitis C virus antibody (HCVAb).

e. A family history of sudden cardiac or unexplained death.

f. Any condition or abnormal laboratory finding that could result in harm to the subject, affect the outcome of the study, or suggest unstable medical illness.

g. As a result of the MINI, medical history, physical examination, and/or screening investigations (including ECG results, vital signs and/or laboratory abnormality), an Investigator considers the subject disqualified for the study.

h. Subject plans to undergo elective procedures/surgery at any time during the study.

i. Subject has had surgery within the past 90 days.

j. Subject of child-bearing potential is pregnant or planning to become pregnant during the duration of the study or within 30 days of the end of the study.

k. Subject is breast-feeding during the study or within 30 days of the study.

2. Medications

a. Subject has taken any medication that, in the opinion of an Investigator, has been shown to alter the PK of d-MPH.

b. Use of any prescription medication within 14 days prior to Day -4 (ADHD medications must be discontinued at least 96 hours prior to check-in at Day -4), and/or use of any OTC medications (such as antacids, vitamins, minerals, dietary/herbal preparations, and nutritional supplements) within 7 days prior to Day -3 unless jointly approved by an Investigator and Sponsor.
   i. Subjects are permitted to take hormonal contraceptives and hormone replacement therapy at acceptable levels if stable at least 30 days prior to Day -4, through the duration of the study, and for 30 days after the study ends.
   ii. Acetaminophen (up to 2 grams per day) may be used during the study under the direction of the Investigator.
   iii. On a case-by-case basis, an Investigator is permitted to allow the use of certain concomitant medications, for example, to treat an AE, as long as an Investigator determines that the medication will not affect the subject's safety or study integrity (eg, topical medications).

3. Alcohol/Substance Abuse

a. Recent history (within the last year) of alcohol or other substance abuse.

b. Subject has positive breath alcohol test or urine test for drugs of abuse at screening or check-in (except THC). Prescribed ADHD medication is acceptable during screening but must be stopped at least 96 hrs prior to check in at Day -4. Note: At the discretion of an Investigator, the tests may be repeated. If THC is positive at screening or check-in, a cannabis intoxication evaluation will be done by an investigator at check-in on Day -4; inclusion will be at the investigator's discretion, due to the slow release of THC from adipose tissue.

4. Smoking

a. Subject regularly smokes more than 10 cigarettes/day (or other nicotine-containing products) or Subject has recently discontinued smoking (within the last 3 months)

5. Allergy/Intolerance

a. Subject has a history of allergy to d-MPH, to any component of the dosage form, or any other allergy, which, in the opinion of an Investigator, contraindicates their participation.

6. Clinical Studies

a. Participation in another investigational product study (inclusive of final post-study examination) or receipt of an investigational drug within the 30 days before screening day.

b. Previous participation in this study.

7. Personnel

a. An employee of the sponsor, study site, or members of their immediate family.

8. Blood

a. Subject has donated blood, plasma, or experienced significant blood loss (excess of 500 ml) within 3 months of screening and for the duration of the study.

4.5 SUBJECT WITHDRAWAL CRITERIA

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

Should a subject decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible. Regardless of the reason for withdrawal, a complete final evaluation should be made at the time of withdrawal following the procedures of EOS, including a final PK draw and an explanation of why the subject is withdrawing from the study. All reasons for early withdrawal must be recorded.

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

4.6 SUBJECT REPLACEMENT

Approximately 36 subjects will be randomized in order to achieve the target of 32 evaluable subjects completing the entire study. Subjects that early terminate, or otherwise have insufficient blood concentration data as to be evaluable, may be replaced at the discretion of the Sponsor. All subjects treated with at least one dose will be evaluated for the safety population. All subjects who receive at least one study treatment and complete at least one PK blood draw will be included in PK analysis.

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. It is assumed that each cohort will randomize approximately 6-12 subjects to allow for a recruitment total of approximately 36 completers and at least 32 evaluable subjects. . Subsequent cohorts will accommodate for dropouts should any subjects be identified as not evaluable. At the end of the third cohort, enrollment may be evaluated for completeness (e.g. 32 evaluable, 8 per sequence, for planned comparisions) by an unblinded biostatistician otherwise not involved in study conduct. If the required number of evaluable subjects is not achieved, the study may proceed with additional cohort recruitment.

4.7 SUBJECT RESTRICTIONS

4.7.1 Lifestyle

- Subjects must be able to fast for at least 10 hrs prior to dosing and at least 4 hours post-dose for the tolerability test (Day -3) and for each Assessment Day (Day 0, 3, 6, and 9).
- Subjects must not consume any fluids for at least 1 hr. prior to dosing and at least 2 hrs following dosing, excluding the 240 mL of water administered with the dose.
- Subjects must be able to refrain from smoking 1 hour prior to dosing and 7 hours post dose. Subject must not smoke more than 1 cigaratte per hour, not to exceed 10 cigarettes per day.
- Subjects must abstain from alcohol consumption for 48 hrs prior to check in at Day -4 and for the duration of the study.
- Subjects must not consume any caffeine or xanthine-containing beverages or foods (e.g., tea, coffee, chocolate, cola) for at least 10 hrs prior to Day -4 and for the duration of the study.
- Subject has donated blood, plasma, or experienced significant blood loss (excess of 500 ml) within 3 months of screening and for the duration of the study.

4.7.2 Medications and treatments

- Subjects must discontinue all ADHD medications at least 96 hrs prior to check in at Day -4.
- Subjects must not use prescription medication within 14 days prior to Day -4 (ADHD medications must be discontinued at least 96 hours prior to Day -4) and/or use any OTC medications (such as antacids, vitamins, minerals, dietary/herbal preparations, and nutritional supplements) within 7 days prior to Day -3, unless jointly approved by an Investigator and Sponsor.

Subjects will be questioned on compliance with restrictions prior to commencement of each assessment day. An Investigator, with approval from the Medical Monitor, will determine ongoing eligibility and whether a deviation from the restrictions warrants the subject's withdrawal from the study. All deviations should be documented in the source document and eCRF.

5 STUDY TREATMENTS: ASSIGNMENT & SUPPLY MANAGEMENT

5.1 STUDY TREATMENTS

5.1.1 Identity of study treatments

An unblinded clinical staff member will dispense the following treatments according to a pre-defined randomization schedule provided by the Sponsor. All treatments will be dispensed in a blinded, closed-lid cup to blind the subjects and the study staff. The treatments administered during the study are as follows:

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

Trimodal d-MPH tablet

Standard pharmaceutical excipients will be used during the manufacturing of the tablets. The dose of d-MPH in each tablet will be either 6.25 mg or 50 mg of CTx-1301.

Focalin™ XR Extended-Release Capsule
This marketed product is a hard gelatin capsule. The dose of d-MPH in each capsule will be either 5 mg or 40 mg for the Extended Release. Further pharmaceutical information is available in the Package Insert.

5.1.2 Selection of doses

Each subject will receive (1) dose of all four treatment arms according to the sequence they are randomized to (see Table 6). All sequences include 1 dose of: Focalin XR 5 mg, CTx-1301 6.25 mg, Focalin XR 40 mg, and CTx-1301 50 mg.

5.1.3 Administration

The investigational drug and reference drug will be administered to the subjects by an unblinded clinical staff member of the study site and the administration will be witnessed by a second unblinded member of clinical staff.

The subjects will be blinded to the dose by way of a blinded dosing cup. Subjects will be dosed sitting down and instructed to swallow the dose with 240 ml of room-temperature water; all 240 mls of water must be consumed within 60 seconds of swallowing the dose. A mouth check should be done to ensure the subject swallowed the dose. The investigational and reference drugs may not be crushed, chewed, or altered in anyway. Subjects must swallow the study drug whole, as provided. After dosing, subjects will remain seated upright (no reclining) for at least 2 hours (hrs 0-2) and seated upright and/or ambulatory for hrs 2-4, unless position needs to be adjusted for an AE. Subjects are allowed to move during hrs 0-4 if required for study-related procedures, or to use the bathroom. The subjects will have restricted activity throughout the study so as to not increase heart rate by physical exertion. Subject are not allowed to engage in any vigorous activity throughout the study.

Study treatment and timing of administration will be documented in the source documents and eCRFs. Any deviation from the protocol-specified dosing regimen and activity restrictions must be recorded.

Trained study site personnel will be onsite for the duration of the Tolerability Test Day and Assessment Days.

The unblinded clinical staff will include clinical staff administering and witnessing the dosing, conducting the mouth check, and the unblinded pharmacy staff. The unblinded clinical staff will ensure subjects were randomized to the correct sequence and dosed as randomized.

All investigators and other study staff will remain blinded throughout the study.

5.1.4 Dose schedule

All treatments, including the Tolerability test and Assessment Day treatments, will be dosed in the morning (by approximately 8:30 am); all subjects must be dosed within approximately 60 minutes of each other. Subjects will have fasted in-clinic for at least 10 hrs prior to each dosing period and at least 4 hours post-dose. Fluids, including water, are restricted at least 1 hr. prior to dosing and at least 2 hrs after dosing; the 240 mL of room-temperature water with dosing is allowed and required per protocol.

Subjects will be dosed as per the schedule described in Table 2 in a randomized sequence.

There will be a 72-hour washout (3 days) between each dosing/Assessment day.

5.1.5 Dose modification

No dose modification is permitted in this study.

5.1.6 Treatment compliance

A record of the administration of study products will be kept using the Investigational Product(s) Dispensing and Accountability Record and the source documents; any comments on the performance of this procedure should be recorded on the source document and eCRF.

Any violation of compliance will require evaluation by an Investigator and Sponsor to determine if the subject will continue in the study.

5.1.7 Precautions

No special precautions are necessary provided that the study is conducted according to this protocol. The Principal Investigator is responsible to oversee the medical well-being of the subjects during the course of the study. Ongoing monitoring days will be conducted by the sponsor-appointed CRO to ensure compliance to the protocol.

5.1.8 Over-dosage

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol.

Overdose *per se* is not an AE; it should be recorded as a protocol deviation and the CRO/Sponsor should be notified immediately. However, any clinical sequelae of an overdose should be reported as an AE (and an SAE, if appropriate). See Section 9.1.2 for reporting instructions.

It is unlikely that over-dosage will occur in this study as treatments are prepared on an individual basis according to an approved manufacturing protocol and administered by clinical staff, not by the subjects themselves.

5.1.9 Rescue therapy

No rescue therapy is applicable for this study.

5.1.10 Risks

The perceived risks involved in this study relate to:

Drug

The study population may not benefit from the single-dose treatment at each day. Inclusion and exclusion criteria have been chosen in order to enable a uniform study population and to minimize possible risks in relation to the administration of CTx-1301 tablet and Focalin™ XR Extended-Release capsule.

The most common adverse reactions after taking Focalin™ XR Extended Release capsules (at least 5% and twice the incidence among placebo-treated subjects) are dry mouth, dyspepsia, headache, and anxiety for adult subjects. Adverse reactions are expected to be similar for both CTx-1301 and Focalin™ XR based on a pilot study for CTx-1301.

Table 7 shows the treatment-emergent adverse events resulting from a placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30 and 40 mg per day. Only events that occurred in 5% or more of the subjects and for which the incidences appear to increase with dose are reported.

Table 7: Treatment-Emergent Adverse Events Occurring during Double-Blind Treatment (Adults)

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

Two other adverse reactions occurring in clinical studies with Focalin XR at a frequency greater than placebo, but which were not dose related were: feeling jittery (12% and 2%, respectively) and dizziness (6% and 2%, respectively).

Nervousness and insomnia are the most common adverse reactions reported with other Methylphenidate HCl Dosage Forms. The following adverse reactions may also occur:

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

Gastrointestinal: abdominal pain, nausea

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

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

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

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

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

Blood/Lymphatic: leukopenia and/or anemia

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

Psychiatric: transient depressed mood, aggressive behavior, libido changes

Skin/Subcutaneous: scalp hair loss

Urogenital: priapism

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

Further information can be found in the Focalin™ XR Extended-Release Package Insert.

Blood Sampling

Blood samples will be taken for safety and/or pharmacokinetic assessments during screening and follow-up medical examinations as well as on Assessment Days. There is a risk of bruising and fainting during blood sampling.

Direct venipuncture or cannula (small plastic tube) may be used to obtain PK samples. This may be a little uncomfortable and may leave a bruise. A cannula may be used because it allows several blood samples to be drawn without the need to insert a needle in the subject's arm each time. The cannula may remain in place for the duration of the Assessment Day but may need to be re-sited during this time. There is a very small risk of inflammation of the vein and changes in the sensation in the subject's arm following blood sampling.

If blood sampling via venipuncture is not possible, and/or not preferred, a cannula will be inserted by study staff. Use of venipunctures and/or cannulas should be recorded in the CRFs.

5.2 STUDY SCREENING PROCEDURE AND TREATMENT ASSIGNMENT

5.2.1 Screening procedure

A unique screening number will identify all subjects screened for study participation. Screening numbers will be noted with an “S” followed by three digits, assigned in ascending numerical and sequential order, according to appearance at the study site, e.g. S-001, S-002, etc. All subjects that consent must be assigned a screening number. A subject who screen fails prior to, or on Day -4 , but may still be a suitable candidate for the study, may be rescreened. Subjects who are rescreened will be assigned a new screening number.

Screening numbers must be maintained by the study staff in the source documents and eCRF.

5.2.2 Randomization procedure

This is a randomized study. Subjects should only be enrolled and randomized if they meet inclusion/exclusion 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. The subject enrollment/randomization numbers correspond to a pre-defined randomization schedule prepared by the Sponsor. Subject enrollment numbers will be assigned in ascending numerical order per cohort as enrolled. 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 and initial randomization numbers. If a subject early terminates that enrollment/randomization number must still remain attached to the early termination subject. If an initial randomization sequence is skipped, the unblinded pharmacist (or unblinded qualified pharmacy staff) must immediately consult with the unblinded statistician at the CRO for next steps.

Following the completion of the planned cohorts and replacement assignments, an unblinded statistician may review the allocations as described in Section 4.6.

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

5.2.3 Blinding procedure

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. A second verification by an unblinded study member will be conducted to ensure the enrolled subjects are randomized to the correct randomization sequence per the subject enrollment/randomization number and ensure that the correct treatment was provided on each treatment day. The 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 staff blinded.

Note: The tolerability dose on Day -3 is unblinded and may be administered by a member of the protocol-trained clinical staff.

As described in Section 4.6, an unblinded statistician not involved in study conduct may review subject randomization allocations following the completion of initial and replacement assignments.

5.3 STUDY TREATMENT SUPPLIES MANAGEMENT

5.3.1 Manufacture, Packaging and Labeling

Manufacture, packaging and labeling of all study treatments will be carried out by a qualified vendor.

All CTx-1301 Investigational drug will be provided in 100-ct, white plastic bottles, and will be labeled as specified with the following information: study number, investigational drug name, batch number, count, storage requirements, manufacturing information, and "Caution: New Drug--Limited by Federal (or United States) Law to Investigational Use."

Focalin™ XR Extended Release Capsules are a commercially marketed product and will be provided by and sourced by the Phase I unit. The clinical site will place a label on the bottle stating: Protocol Number CTx-1301-001, For Clinical Trial Use Only.

5.3.2 Accountability of study supplies

The unblinded study pharmacist, or designee, will maintain a full record of study treatment accountability. A second unblinded clinical staff member must double check correct randomization sequence and correct accountability. An Investigational Product Dispensing and Accountability Record should be kept up to date with the following information:

- The identification of the subject to whom the study treatment was dispensed.
- The time, date, and assigned treatment and sequence of the study treatment dispensed to the subject.

In order to comply with FDA rules and regulations, the clinical research unit will retain an adequate quantity of reserve samples for the test and reference formulations that shall permit, if required, to perform 5 times all of the release tests required in the application or supplemental application (New Drug Application [NDA's] or Abbreviated New Drug Application [ANDA's]). The labeling, storage conditions and retention period of the reserve samples shall comply with the current version of FDA regulation 21 Code of Federal Regulations (CFR) section 320.38 and/or 320.63 and the May 2004 FDA guidance Handling and Retention of BA and BE Testing Samples.

At the end of the study, all study supplies should be reconciled with this record. Any unused materials that are not retained as reserve samples must be maintained at the study site and returned or destroyed as directed by the sponsor.

5.3.3 Storage of study treatment supplies

Study drug must be held at USP controlled-room temperature of 20-25°C.

Throughout the duration of the study, all study medication will be securely stored within the pharmacy. The pharmacy is monitored by the REEs system, which provides continuous temperature monitoring and alerts the pharmacy staff prior to a temperature deviation.

If a temperature or storage deviation occurs, the CRO and Sponsor should be alerted immediately. Sponsor will determine if excursion falls within acceptable stability limits or if drug should be quarantined.

6 STUDY SCHEDULE

The summary of the Study Schedule (Table 2) includes a detailed schedule for the tolerability test day (Table 3) and assessment days (Table 4).

7 SCREENING AND BASELINE METHODS, MEASUREMENTS AND EVALUATIONS

7.1 SCREENING

7.1.1 Informed consent

An Investigator, or medically qualified designee, must obtain written (signed and dated by the subject) informed consent from each subject, participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

An Investigator, or medically qualified designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the Sponsor or designated CRO. An Investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly.

The subject will be provided with a copy of their signed and dated consent form, along with any other written information, which they should be instructed to retain. The original informed consent must be stored in the regulatory file for the study. All subjects that complete an ICF must have an assigned screening number.

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

7.1.2 Demographics

An Investigator, or designee, will record each subject's date of birth, gender, and race in the source documents and eCRF.

7.1.3 Medical history

An Investigator, or medically qualified designee, will take a medical history from each subject. Details of any relevant medical or surgical history, including allergies, drug sensitivity, and previous ADHD treatments will be recorded. All concomitant medications will also be recorded.

7.1.4 Physical examination

An Investigator, or medically qualified designee, will perform the physical examination at specified time-points according to the Study Schedule, which will include assessment of the following body systems: central nervous system (CNS); eyes; ears, nose and throat (ENT); respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine/metabolic; hematopoietic/lymphatic; and dermatological.

The outcome of these assessments will be documented in the source document and eCRF and any abnormalities will be described. If any abnormalities are observed, they will be recorded as medical history or AEs, pending timing of observation.

7.1.5 ECG

An Investigator will read all ECGs and evaluate for clinical significance. If investigator deems the ECG abnormal, a cardiologist will conduct an overread and the Investigator will discuss with the Medical Monitor.

7.1.6 MINI Version 7.0.2 and C-SSRS

An Investigator, or medically qualified designee, will perform a mental state examination and suicide assessment at specified time-points according to the Study Schedule, which will include assessment of potential psychosis, mania and suicidal thinking. The C-SSRS Baseline version will be administered at screening and the C-SSRS Since Last Visit will be administered at subsequence time-points.

The outcome of these assessments will be documented in the source document and eCRF. Any potential subject deemed to be at risk will be excluded from the study.

7.1.7 Body mass index (BMI)

Height (cm) and weight (kg) will be measured and recorded in the CRF. BMI will then be calculated as follows:

$$BMI = (Weight\ (kg) / (Height\ (cm)^2) \times 10{,}000.$$

BMI must be between 18.0 – 35.0 inclusive to be eligible for study participation.

7.1.8 Vital signs

Arterial blood pressure and heart rate will be recorded at screening and at specified time-points according to the Study Schedule when subjects are resting in a sitting position for a minimum of 5 minutes; vital signs and time must be recorded in the source document and eCRF.

Data must be collected in the source and eCRFs. If Blood Pressure window overlaps with PK window, BP should be taken prior to PK draw.

Vital signs should be taken at the protocol-specified time (± 10 minutes) for the tolerability day, assessment/treatment days, and non-treatment days.

An Investigator can interpret individual findings based on the subject's age, physical state and level of fitness. Subjects with vital signs outside the normal range which, in the investigator's opinion, are not clinically significant and would not affect the subject's safety during the study may be included; this decision will be documented in the source document and eCRF.

7.1.9 Clinical laboratory tests

An Investigator, or appropriately qualified designee, will collect blood samples for hematology, biochemistry analysis, and TSH at screening and check-in (Day -4). Blood samples for serology (HIV, HBsAg, and HCV antibody) will be taken at screening only. Urine samples for urinalysis will be collected at screening, check-in at Day -4, and EOS/ET. A woman will be considered to have no child-bearing potential if they are surgically sterile (hysterectomy, tubal ligation, or endometrial ligation) or post-menopausal (12 months since last menses). For women of child-bearing potential, serum HCG will be collected/analyzed at screening, check-in (Day -4), and EOS/ET. Values for the laboratory safety tests must be within normal ranges (as defined by an accredited laboratory facility) or considered not clinically significant (NCS) by a medically qualified designee for the subject to be eligible for the study. The results of all tests conducted at Day -4 must be available and reviewed before the tolerability day on Day -3.

Blood samples for hematology, biochemistry, TSH, and urine samples for urinalysis will be repeated at the EOS visit and should be reviewed for clinically significant changes from screening; if clinically significant changes are observed, they should be recorded as AEs.

The following tests will be carried out:

Hematology
White Blood Cell (WBC) and differential, Red Blood Cell (RBC), Hemoglobin (Hb), Hematocrit (Hct), Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH) and platelets.

Biochemistry
Sodium, potassium, chloride, BUN, creatinine, alkaline phosphatase, bilirubin, albumin, adjusted calcium, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), glucose and urate.

Thyroid
Thyroid Stimulating Hormone (TSH)

Serology
HIV-1, HIV-2, Hep-B, and Hep-C

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

All subjects with any clinically significant laboratory finding or other significance will not be eligible for the study and will be advised to follow up with their own PCP or walk-in clinic.

7.1.10 Breath alcohol test and serum screen for pregnancy and drugs of abuse

Urine samples will be tested at screening and check-in at Day -4 for levels of the following drugs of abuse: amphetamines, methylphenidate, benzodiazepines, cocaine, methamphetamine and morphine/opiates. THC will also be assessed for abuse but will be considered exclusionary at the discretion of the investigator. A breath alcohol test will also be performed at screening and check-in at Day -4.

Subjects testing positive for any exclusionary substances (other than ADHD prescribed medication) at screening or at check in on Day -4 must not be enrolled in the study. Subjects that test positive for amphetamine or methylphenidate at screening must agree to washout of the ADHD medication 96 hrs. prior to check in at Day -4 and for the duration of the study. ADHD subjects must test negative for all ADHD medications at check-in on Day -4 to be eligible for the study. If THC is positive at screening or check-in, a cannabis intoxication evaluation will be done by an investigator at check-in on Day -4; inclusion will be at the investigator's discretion, due to the slow release of THC from adipose tissue.

All women of child-bearing potential will have a serum HCG test at screening, check in on Day -4, and EOS/ET; HCG must be negative to be eligible for the study.

Repeat urine analysis may be conducted at the discretion of an Investigator. Investigator may also opt to conduct a urine screen at an unscheduled day to ensure compliance with the protocol.

7.2 SUBJECT CONTINUED ELIGIBILITY ASSESSMENT

Prior to participation in each Assessment Day, an Investigator, or designee, will assess the subject's continued eligibility for the study by confirming the subject still meets the entry criteria on the Assessment Day, as outlined in Sections 4.3 and 4.4, and has adhered to the restrictions outlined in Section 4.7.

7.3 MEAL SCHEDULE

During the Assessment Days, subjects will not be allowed any food or drinks other than those provided by the study site staff.

Subjects will be given lunch at approximately 4 hr., a snack at approximately 6 hr., dinner at approximately 9 hr., another snack at approximately 12 hr., and breakfast at approximately 24 hr. post-dose, respectively. Meal times are approximate and should be evaluated in regard to other protocol-specified evaluations.

Water will be available *ad libitum* from at least 2 hr. post-dose and decaffeinated fluids will be available *ad libitum* from approximately 9 hr. post-dose on assessment days.

7.4 EARLY TERMINATION DAY

The early termination visit should follow the same study schedule as EOS day, and include a final PK draw if possible. Every effort should be made to obtain as much information as possible if a subject early terminates. An Investigator should contact the medical monitor if subject is discontinued for any reason.

7.5 DURATION OF THE STUDY

The study will be conducted over the course of approximately 4-6 weeks from screening to completion for each subject. Subjects will remain in-clinic from Day -4 through EOS for a total of 15 days in-clinic.

The end of the clinical phase of the study will be defined as last subject, last day in clinic (EOS).

8 PHARMACOKINETICS

8.1 PHARMACOKINETIC BLOOD SAMPLING

At each Assessment Day blood samples will be drawn by suitably trained site staff using an indwelling cannula or by venipuncture at appropriate time-points to allow an assessment of methylphenidate concentrations in the plasma. PK draws should be in the same arm throughout the study, if possible. The arm used for PK draws should be recorded for each PK timepoint.

The total blood volume taken at each time-point will be approximately 5 mL (4 mL sample volume and 1 mL waste volume). There is a risk of bruising and fainting during the blood sampling procedure. See AE section for reporting procedure-related AEs.

A pre-dose (0) blood sample will be taken no more than 60 minutes prior to dosing. Blood samples will then be withdrawn at specified intervals: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 24, and 28 hr. post-dose.

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

The actual sample times (times samples actually taken) should be recorded on the Blood Sampling Source Document and should be entered at the time of sampling. Time collected should be reported as the start of the sampling collection, defined as the actual drawing of blood volume. The actual times must be recorded in the 24-hr format. Any blood sample taken more than ±5 min outside of the set sampling times will be recorded as a protocol deviation.

8.2 BIOANALYSIS OF PLASMA SAMPLES

The analysis of these samples will be undertaken by a Sponsor-approved laboratory. Blood samples for PK determination will be processed, split, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility. Samples will be evaluated using a validated d-MPH method (see Bioanalytical Plan for further information on collection, methods, and validation).

Pharmacokinetic metrics to be evaluated are: $AUC_{0\text{-}inf}$, AUC_{last}, K, $T_{1/2}$, C_{max}, t_{max}, and t_{lag}, including partial AUCs ($AUC_{0\text{-}3}$, $AUC_{3\text{-}6}$, $AUC_{6\text{-}9}$, $AUC_{9\text{-}12}$, and $AUC_{12\text{-}16}$). Graphical analysis will use protocol-stated times. PK analysis will use exact blood draw time, defined above.

Additional parameters may also be calculated if considered appropriate.

9 SAFETY MEASUREMENTS AND EVALUATIONS

9.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

An Investigator and site staff are responsible for detecting, documenting, and reporting events that meet the definition of an Adverse Event (AE), Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.1.1 Definitions

Adverse event

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of an investigational product whether or not considered related to the investigational product.

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

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

- Exacerbation (worsening) of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.

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

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

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

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

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

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

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

- Pregnancy (of a study subject or partner of a study subject), although any medical conditions arising from pregnancy may be classed as an AE.

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

Serious adverse event

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

a) Results in death.

b) Is life-threatening.

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

c) Requires hospitalization or prolongation of existing hospitalization.

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

If hospitalization occurs due to an elective treatment of a pre-existing condition which did not worsen from baseline, it is not considered an AE.

d) Results in disability/incapacity, or

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

e) Is a congenital anomaly/birth defect.

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

9.1.2 Reporting adverse events and serious adverse events

Time period for reporting adverse events and serious adverse events

AEs will be collected from the time the subject consents. AEs collected between consent and prior to randomization should be evaluated to determine if attributed to study procedure, tolerability dose, or prior medical condition since test drug has not yet been administered. Assessments obtained at Screening should be recorded as medical history unless related to study procedure. AEs collected after randomization should be evaluated for relatedness to study drug, study procedures, or both. AEs will be assessed until the end of the study (EOS), early termination (if applicable), or until resolved or stabilized.

SAEs will be collected over the same time period and same process as stated for AEs. SAEs should be evaluated by the PI as related to study drug or study procedures. Scientific rationale for attribution to drug or procedures should be recorded in the source document and eCRF. SAEs must be reported to the Sponsor within 24 hrs of an Investigator or designee becoming aware of the situation.

Medical conditions existing prior to consent should be recorded as part of the subject's medical history. Medical conditions that are exacerbated while on study should be evaluated as to normal fluctuation of disease state or relation to study drug or procedure.

Reporting adverse events

Adverse events can be reported at any time while on study and site should record in the AE source document as well as the AE section of the eCRF.

Any new medical conditions not present prior to participation in the study reported by the subject which meet the definition of an AE (described above) should be recorded as stated above. AEs must be recorded in detail on both the AE source document and in the eCRF. If the same AE occurs multiple times, the AE is to be recorded for each occurrence. AEs should also be recorded as reported.

After randomization on Day 0, AEs will be evaluated for relation to study drug or study procedure.

9.1.3 Adverse event grading and assessments

Intensity grading

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

- Mild – easily tolerated, causing minimal discomfort and not interfering with normal everyday activities

- Moderate – sufficiently discomforting to interfere with normal everyday activities

- Severe – incapacitating and/or prevents normal everyday activities

Relationship assessment

Study drug or study procedure relationship for each AE should be determined by an Investigator using the following rationale and explanations:

- Not related to Study Drug
    - The AE does not follow a reasonable temporal sequence from investigational product administration or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

- Related to Study Drug
    - The AE follows a reasonable temporal sequence from the investigational product administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications).
    - The AE follows a reasonable temporal sequence from the investigational product administration and represents a known reaction to the investigational product under study or other drugs in its class or is predicted by the known pharmacological properties of the drug.
    - The AE resolves with discontinuation of the investigational product and/or recurs with rechallenge, if applicable.

- Procedure related
    - The event is not related to the study drug but is related to the subject's participation in the study in another capacity, for example: bruising due to venipuncture or intolerability of Focalin XR 40 mg at tolerability day.

Duration

Start and end-dates of the adverse event will be recorded.

Follow-up

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

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

Reporting serious adverse events

A copy of the SAE report form provided in the regulatory site file should be completed as fully as possible and must be reported within 24 hours of first learning of the SAE to CRO via the following SAE fax/e-mail address. Additionally, the SAE should be recorded into the EDC.

Table 8

Premier Research Pharmacovigilance	
Email	GlobalPV-US@premier-research.com
Fax number	+1 215-972-8765

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study treatment or study procedure
- Criterion for seriousness

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

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

The initial report will be followed up with more information as relevant. This may require an Investigator to obtain copies of hospital case reports, autopsy reports and other documents as applicable. If CRO or Sponsor request copies of any subject-identifying information such as hospital forms, the forms should be redacted, and the subject number should be written on the forms for study identification.

Reporting of SUSARs

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

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

> *SUSARs which are fatal or life-threatening*: reporting to the Ethics Committee and FDA within 7 days of becoming aware of the event. A more detailed report will be provided within an additional 8 days.
>
> *All other SUSARs*: reporting to the Ethics Committee and FDA within 15 days of first becoming aware of the event.

9.2 PREGNANCY

9.2.1 Time period for collecting pregnancy information

All women of child-bearing potential will require a serum HCG test at screening, check-in at Day -4, and EOS/ET. All subjects of child-bearing potential must use a double-barrier method form of birth control or meet other birth control methods as defined per protocol, while on study. Females that are confirmed pregnant during screening and/or before randomization are excluded from the study. Females that are breastfeeding during screening and/or before randomization, and/or for 30 days following the study, are excluded from the study.

9.2.2 Action to be taken if pregnancy occurs

The Investigator, or designee, will record pregnancy information on the appropriate pregnancy data collection form and submit it to the CRO within 24 hours of learning of the pregnancy.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE as defined in Section 9.1.2. Note that termination itself is not an AE, only any medical reasons for a termination should be recorded as an AE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the Investigator's attention after the subject completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly recorded.

The Investigator, or designees, should report pregnancy only, or pregnancy with an associated SAE, immediately to the CRO via the following fax/e-mail address.

Premier Research Pharmacovigilance	
Email	GlobalPV-US@premier-research.com
Fax number	+1 215-972-8765

9.3 LABORATORY EVALUATIONS RELATED TO SAFETY

Clinical safety laboratory assessments (hematology, biochemistry and urinalysis) will be conducted during the screening day and at check-in (Day -4) to ensure the subject's good health. Subjects with clinically significant labs at screening and/or at check-in (Day -4), as assessed by an Investigator, should not be enrolled in the study. Clinical safety laboratory assessments will be repeated at EOS (or ET day, if applicable) to ensure the subject's health has not been adversely affected by their participation in this study. Abnormal results detected at EOS (or ET day, if applicable) which differ from check-in labs (Day -4) and the Investigator considers to be clinically significant, will be recorded as an AE.

Clinically significant findings in laboratory tests at screening and/or at check-in on Day -4, will be considered pre-existing conditions (medical history), as well as failure to meet eligibility criteria; they will not be considered AEs. However, for any medical event or condition discovered at screening, which, in the opinion of an investigator, is significant enough to be followed up externally, subject will be asked to follow up with their primary care physician.

9.4 VITAL SIGNS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs will be assessed at screening, the tolerability day for Focalin XR 40 mg, at each Assessment Day, and non-assessment days to ensure the subject is, and remains in, good general health. Abnormal findings that the Investigator considers to be clinically significant, other than at screening, will be recorded as an AE.

10 STATISTICAL/DATA ANALYSIS METHODS

10.1 GENERAL CONSIDERATIONS

This section describes the rules and conventions to be used in the presentation and analysis of the data. A comprehensive presentation of the data management plan and statistical analysis plan will be approved by the Sponsor prior to PK analysis and unblinding of the study data.

10.2 STATISTICAL AND ANALYTICAL PLAN

This is a randomized, single-dose, four-sequence, four-period, in-clinic crossover PK study to evaluate PK concentrations of d-MPH in the investigational drug compared to the registered listed drug (RLD) under fasted conditions.

The following variables will be assessed over the course of the study, by day and time: $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}, including partial AUCs ($AUC_{0\text{-}3}$, $AUC_{3\text{-}6}$, $AUC_{6\text{-}9}$, $AUC_{9\text{-}12}$, and $AUC_{12\text{-}16}$). Additional parameters may also be evaluated.

Safety will be assessed by recording any AEs, concomitant medications, physical exams, vital signs, and ECGs.

10.3 STUDY OBJECTIVES

The primary trial objective is to compare the bioavailability of the marketed product (Focalin XR) to CTx-1301 trimodal investigational product under fasted conditions and demonstrate dose proportionality of CTx-1301.

The secondary trial objectives include evaluation of data on blood plasma levels of d-MPH and to evaluated safety measurements including ECG, vital signs, lab assessments, physical exam, C-SSRS, and occurrence of treatment-emergent adverse events.

10.4 SAMPLE SIZE DETERMINATION

The study design is a randomized, single-dose, four-sequence, four-period, in-clinic crossover study. Cmax, $AUC_{0\text{-}inf}$, 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 the context of a bioavailability analysis, similarity will be concluded if the 90% confidence interval (CI) of the geometric mean ratios for Cmax, AUCinf, AUClast 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% siginicant level. The TOST procedure will identify two treatments as equivalent 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 assumptions, that the bioavailability analysis falls within the 90% CI of [0.80—1.25], a sample size of at least 32 completers will provide at least 88% power with the assumption of within-subject CV (coefficient of variation) of 17-21% and true bioavailability ratio (B/A and D/C) of 93-107%. With assumption of the drop-out rate of 11%, 36 subjects total (6-12 subjects per cohort) will be randomized. No adjustment for multiple comparisons will be made.

10.5 ANALYSIS POPULATIONS

- **Safety Population (SAF**): The SAF Population includes all subjects who receive at least 1 dose of study drug.
- **PK Population**: The PK Population includes all subjects who receive at least 1 dose of study drug and provide at least one evaluable PK plasma concentration.

10.6 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

10.7 PHARMACOKINETIC ANALYSIS

Pharmacokinetic sample analysis will be performed by a central laboratory. The results will be shared with the CRO for the PK parameter calculations and the final PK analysis report.

Pharmacokinetic analysis will be based on PK population. Plasma CTx-1301 and Focalin™ XR concentrations will be summarized descriptively by treatment and nominal sampling time point.

Pharmacokinetic parameters (including $AUC_{0\text{-}inf}$, AUC_{last}, K, $T_{1/2}$, C_{max}, t_{max}, and t_{lag}) will be summarized descriptively by treatment group as appropriate. Partial AUCs and dose-normalized PK parameters (including dose normalized $AUC_{0\text{-}\infty}$, AUC_{last}, C_{max}) will also be calculated (by dividing the nominal dose) and summarized similarly.

Natural log-transformed pharmacokinetic parameters (including $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}) will be analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. A sensitivity analysis may be conducted to analyze any unexpected differences among cohorts. 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 will be obtained from the model. The adjusted mean differences and 90% confidence intervals 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% confidence intervals for the ratios.

Natural log-transformed, dose-normalized, pharmacokinetic parameters (including $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}) will also be analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. A sensitivity analysis may be conducted to analyze any unexpected differences among cohorts. 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 will be obtained from the model. The adjusted mean differences and 90% confidence intervals 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% confidence intervals for the ratios. Dose proportionality will also be evaluated based on the model for dose-normalized parameters, using a ratio of adjusted gometric 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.

Natural log-transformed, dose-normalized, pharmacokinetic parameters (including $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}) will also be analyzed to evaluate dose proportionality of CTx-1301 using the 6.25 mg and 50 mg doses.

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.

Additional details of pharmacokinetic analysis will be included in the statistical analysis plan.

PK plasma concentrations of d-MPH will be summarized by treatment and time point.

10.8 SAFETY ANALYSIS

Safety analysis will be performed for the Safety Population.

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

Adverse events will be classified using Medical Dictionary for Regulatory Activities (MedDRA) classification system. Adverse events will be summarized by treatment Summary for TEAEs will be classified by system organ class, preferred term, severity, and relationship to treatment.

Data for laboratory tests, vital signs, ECG, physical exams and C-SSRS will be summarized descriptively. More details will be provided in the statistical analysis plan (SAP).

11 ETHICAL AND REGULATORY ASPECTS

11.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

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

11.2 INFORMED CONSENT

It is the responsibility of the Investigator, or medically qualified designee, to obtain written (signed and dated by the subject) informed consent from each individual participating in this study. Major/substantial amendments to the protocol that affect the scope of the study at the subject level and/or updates to the safety profile of an investigational product will be reflected in the updated consent form and active subjects will be re-consented. Refer to Section 7.1.1.

11.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

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

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

The outcome of the study (e.g. completed) will be reported to the IEC/IRB responsible for the study within 90 days of completion of the last subject's final study procedures. In the event of the study being prematurely terminated, a report will be submitted to the IEC/IRB responsible for the study within 15 days.

11.4 FUNDING

The study is funded by the Sponsor, Cingulate Therapeutics.

12 STUDY REPORT, DOCUMENTATION, CRFS, PUBLICATION, AND RECORD KEEPING

12.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into

two categories: (1) Study Regulatory file, and (2) study/subject clinical source documents (including CRF). The site's regulatory file must be held at the study site for as long as needed to comply with national and international regulations. The Sponsor will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

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

12.2 SOURCE DOCUMENTS/DATA

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

12.3 CASE REPORT FORMS

For each subject who has given informed consent, an eCRF must be completed and signed by the Principal Investigator to certify that all collected data are complete and correct. This also applies to those subjects who are screened but not entered into the study. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be clearly made to document the outcome and provide the reason for withdrawal from the study as an AE in the eCRF.

All source documents should be completed during (or immediately after) a subject assessment. Source documents should be completed in a GCP-compliant manner. The text should be written with a black or blue ballpoint pen and must be legible. If a source document entry needs correction, the error should be crossed out with a single line (not obliterated or covered with correction fluid) and the correct information should be written next to the original entry. The change must be initialed and dated by the Investigator or designee.

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

12.4 CLINICAL STUDY REPORT AND PUBLICATION POLICY

An ICH-compliant clinical and statistical study report will be written after completion of the study and data analysis. The results of the study may be published in a relevant peer-reviewed journal by the Sponsor, without regard for status and ranking of contributors. Contributions of the participating investigators, institutions, CRO, and Sponsor will be listed, unless otherwise requested.

13 PROCESS FOR AMENDING THE PROTOCOL

All major/substantial protocol modifications must be reviewed and approved by an appropriate IEC/IRB. Approval from the IEC/IRB must be received before the revised edition can be implemented.

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

14 CONDITIONS FOR TERMINATING THE STUDY

It is agreed that for reasonable cause, the Sponsor may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination and provided to each investigator. If the study is terminated prematurely or suspended, the IEC/IRB will be informed and provided with the reason(s) for termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement.

If a drug-related SUSAR occurs at any time during the study, the Medical Monitor and Sponsor will review the case immediately.

The study will not be restarted until all parties have agreed to the course of action to be taken and the IRB/EC has been notified.

If terminating the study, the Sponsor will assure that adequate consideration is given to the protection of the Subject's interests.

15 CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subjects' anonymity is maintained. Subjects should not be identified by their names or initials on eCRFs, but by a subject identification code (screening number or subject enrollment/randomization number).

The Investigator should keep a separate log of subjects' codes and names. Documents which may identify the subject, e.g., subjects' written consent forms, hospital records, etc. will be maintained in strict confidence. Any electronic files that contain subjects' personal data will be appropriately encrypted.

16 AUDITS/INSPECTIONS

The Investigator and study subjects should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source documents (where permitted by law) or through an interview exchange.

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