Official Title:	**A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CTP-692 as an Adjunctive Treatment in Adult Patients with Schizophrenia**
NCT Number:	NCT04158687
Document Date:	Protocol Amendment 3: 14 April 2020

CTP-692

CP692.2001

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CTP-692 AS AN ADJUNCTIVE TREATMENT IN ADULT PATIENTS WITH SCHIZOPHRENIA

INVESTIGATIONAL PRODUCT (IP):	**CTP-692**
PROTOCOL NUMBER:	**CP692.2001, Amendment # 3**
ORIGINAL PROTOCOL:	29 August 2019
AMENDMENT # 1:	16 October 2019
AMENDMENT # 2:	11 February 2020
AMENDMENT # 3:	14 April 2020
EudraCT NUMBER:	**N/A**
IND NUMBER:	**138,912**
SPONSOR NAME / ADDRESS:	Concert Pharmaceuticals, Inc. 65 Hayden Avenue, Suite 3000N Lexington, MA 02421

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CONCERT SIGNATURE PAGE

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CTP-692 as an Adjunctive Treatment in Adult Patients with Schizophrenia

Protocol Number: CP692.2001

[redacted]

Signature of Concert [redacted] **dd mmm yyyy**

[redacted]

Printed Name of Concert [redacted]

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

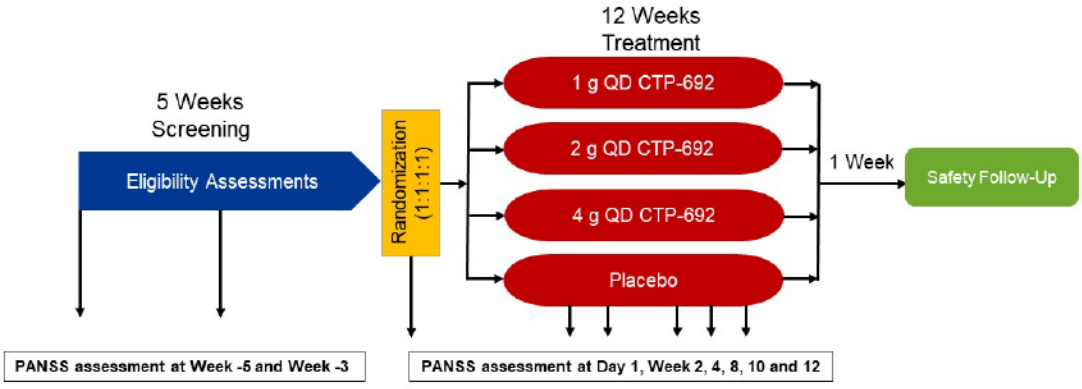
PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CTP-692 as an Adjunctive Treatment in Adult Patients with Schizophrenia

Protocol Number: CP692.2001

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:** By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Boards (IRBs) procedures, instructions from Concert representatives, the Declaration of Helsinki, International Council for Harmonization (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

1. SYNOPSIS

Name of Sponsor/Company: Concert Pharmaceuticals, Inc.	
Name of Investigational Product: CTP-692	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CTP-692 as an Adjunctive Treatment in Adult Patients with Schizophrenia	
Study Center(s): Approximately 22 clinical sites in the US	
Study Duration (years): Approximately 1 year	**Phase of Development:** 2
Objectives: The objective of this study is to assess the safety and efficacy of 3 different doses of CTP-692 administered once daily for 12 weeks to adult patients with schizophrenia on stable dopaminergic antipsychotic medication.	
Study Design and Methodology: This is a randomized, double-blind, parallel group, placebo-controlled, multicenter study. At Screening, potential study participants must have a Diagnostic and Statistical Manual-V (DSM-V) diagnosis of schizophrenia for at least 2 years and confirmed by psychiatric evaluation and MINI International Neuropsychiatric Interview (MINI). The study will involve patient participation for up to 20 weeks and will consist of a 5-week Screening/Qualification Period (this period may be extended up to 2 weeks if repeat laboratory test results for confirmation of eligibility are pending) and a 12-week Treatment Period. A safety follow-up visit will occur approximately 1 week after the last dose of Study Medication. Approximately 300 patients, 18-55 years old, will be randomized to receive 1 of 3 doses of CTP-692 or Placebo. There will be 2 Screening/Qualification Visits: At the first Screening Visit (Week -5) patients will provide informed consent and will be assessed for eligibility based on study inclusion and exclusion criteria, including a total score of 70-110 on the Positive and Negative Syndrome Scale (PANSS). Patients meeting eligibility requirements at the first Screening Visit will undergo an additional in-clinic Qualification Visit approximately 2 weeks after the Screening Visit (at Week -3). Patients who continue to meet eligibility criteria based on assessments through the Screening/Qualification Visits and at Day 1 will be randomized in a 1:1:1:1 ratio to 1 of the 4 treatment groups shown below:	



Note: The Qualification period may be extended up to 2 weeks (after Week -3, prior to Randomization) if repeat laboratory test results for confirmation of eligibility are pending.

Patients will receive their first dose of Study Medication in the clinic on Day 1. Patients will be instructed to take Study Medication at home once-daily (QD) in the morning for the next 12 weeks. Patients will return to the clinic at Weeks 2, 4, 6, 8, 10, and 12 for safety and efficacy assessments and to pick up Study Medication. Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, clinical laboratory blood draws may be performed by a Home Health Care service provider or by a local laboratory; other safety and efficacy assessments may be performed remotely via phone/audio or video conferencing platforms (with the exception of Facebook). Phone contact will be made with the patient on Weeks 1, 3, 5, 7, 9 and 11. The primary outcome measure will be assessed at Week 12. Patients will be required to return to the clinic approximately 1 week after the last dose of Study Medication for safety assessments including physical examination, vital signs, adverse-events and concomitant medications. Due to the COVID-19 pandemic, the Safety Follow-up visit may be conducted remotely via phone/audio or video conferencing platforms (with the exception of Facebook) per Investigator discretion.

Any patient may withdraw from participation in the study at any time. The Investigator may withdraw a patient at any time if they believe the safety of the patient or the integrity of the data are at risk.

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

1. Patient should be able to read, understand and voluntarily sign an informed consent document prior to any study related assessments and procedures being conducted. Patients should be willing to comply with the study visits and requirements of the study protocol.
2. Patient should be between 18 and 55 years of age, inclusive, at the time of signing the informed consent document.
3. Physician confirmed DSM-V diagnosis of schizophrenia for the past 2 years based on patient's history and confirmed by psychiatric evaluation and MINI International Neuropsychiatric Interview for Psychotic Disorders, version 7.0.2 (MINI, Version 7.0.2).
4. The patient is an outpatient with no hospitalization for worsening of schizophrenia within 3 months of the first Screening Visit (Week -5).
5. Patients currently treated with one antipsychotic (AP) medication which has been unchanged (medication and dose) for at least 7 weeks prior to the first Screening Visit (Week -5), and expected to remain unchanged during the Screening and Treatment period. Allowed orally dosed APs are:
    a. Aripiprazole
    b. Asenapine
    c. Brexipiprazole
    d. Cariprazine
    e. Lurasidone
    f. Olanzapine
    g. Paliperidone
    h. Quetiapine
    i. Risperidone

Note: If the patient is being treated with depot or long-acting antipsychotics, they should be on the treatment for at least 2 drug administration cycles prior to the first Screening Visit (Week -5).

6. Patients with confirmed blood levels of their current AP medication in samples drawn at the Qualification Visit (Week -3).

7. The patient has a reliable informant who is able to provide information regarding the patient and support study participation.

8. Patients with clinically stable schizophrenia with residual symptoms defined as PANSS total score of 70-110 per evaluation at the first Screening Visit (Week -5), the Qualification Visit (Week -3) and Day 1.

   Note: At Week -3 and Day 1, the PANSS total score may vary by 10 points as compared to a previous visit, as long as total score remains between 70-110 at each of the three visits for the patient to be included in the study.

   Patients must also meet these additional PANSS criteria:

   a. PANSS score of ≤ 4 on positive scale items of conceptual disorganization and hostility
   b. PANSS score ≥ 4 on **at least <u>two</u>** of the following items:
      i. Delusions
      ii. Hallucinations
      iii. Suspiciousness/Persecution
      iv. Unusual thought content
   c. PANSS Negative Symptom Factor Score (NSFS) ≥ 12

9. If of reproductive age and not infertile (defined below), willing and able to use a medically highly effective form of birth control during the study and for 4 weeks following last dose of Study Medication. Examples of medically highly effective forms of birth control are:
   a. Surgical sterility (via vasectomy, hysterectomy or bilateral ligation) or post-menopausal females (have had spontaneous amenorrhea for at least the last 1 year and at least 1 year after the onset of amenorrhea while not receiving hormone replacement therapy and have a Follicle-Stimulating Hormone (FSH) level greater than 40 mIU/mL)
   b. Sexual partner is sterile, or of the same sex
   c. Implants of levonorgestrel in females
   d. Oral contraceptive (combined or progesterone only) in females
   e. Double-barrier method (any combination of physical and chemical methods)
   f. Intrauterine device in females, or other method with published data showing that the lowest expected failure rate is less than 1% per year

10. Healthy, as determined by the Investigator, based on a medical evaluation including history, physical examination, vital signs, electrocardiogram (ECGs) and clinical laboratory assessments at Week -5.

    Note: A patient with a non-clinically significant abnormality or laboratory parameters outside the reference range may be included only if the Investigator considers that the finding will not

compromise the patient's safety and will not interfere with the study procedures or data interpretation.

11. Body mass index (BMI) within the range of 18 to 40 kg/m^2, inclusive, at the first Screening Visit (Week -5).

Exclusion Criteria:

1. Patients with DSM-V criteria at the first Screening Visit (Week -5) for disorders other than schizophrenia that in the opinion of the Investigator may interfere with study conduct and interpretation of results.
2. Patients who, in the opinion of the Investigator, have a history of antipsychotic treatment resistance.
3. Patients currently taking clozapine.
4. Patients who have been previously treated with or are receiving electroconvulsive therapy (ECT).
5. Patients who have initiated or changed dose of antidepressants or other moods stabilizers within 7 weeks prior to the first Screening Visit (Week -5).
6. Patients currently taking lithium.
7. Patients taking an AP (e.g. Seroquel) as a sleep aid.

   Note: Patients will be allowed to switch to a non-AP sleep aid during the Screening period.
8. Patients who use prescription medications (stimulants) to treat attention deficit hyperactivity disorder or attention deficit disorder.
9. Screening laboratory measurements outside the normal range associated with potential risk for the treatment under investigation at the first Screening Visit (Week -5). This will include but not limited to:
   a. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or total bilirubin > 2x upper limit of normal (ULN)
   b. Estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m^2
   c. Serum creatinine and/or blood urea nitrogen (BUN) > ULN
   d. Urinalysis positive for protein or urine microalbumin/creatinine ratio (UACR) > 30 mg/g

   Note: These laboratory tests may be repeated once, if they are abnormal on first screening, and if there is a medical/analytical reason to believe the results may be inaccurate. If the repeat test is within the reference range, the patient may be included only if the Investigator considers that the previous finding will not compromise the patient's safety and will not interfere with the interpretation of safety data.
10. Patients with suicidal behavior occurring within the past year or who pose a current suicide risk as determined by the PI or as confirmed at the first Screening Visit (Week -5), the Qualification Visit (Week -3) or Day 1 by affirmative answer on items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS).

11. Treatment with an investigational drug within 7 weeks or 5 half-lives (if known), whichever is longer, prior to the first Screening Visit (Week -5).
12. Donation of blood within 4 weeks of Day 1.
13. History of prolonged QT syndrome or a Screening QTc interval with Fridericia's correction (QTcF) > 450 msec for males or QTcF > 470 msec for females.
14. Females who are nursing, pregnant, or planning to become pregnant while in the study and for 4 weeks after the last dose of Study Medication.
15. History of meeting DSM-5 criteria for moderate to severe alcohol or substance use disorder (other than nicotine or caffeine) within the 6 months before the first Screening Visit (Week -5).
16. Positive alcohol breath test.

    Note: A repeat alcohol breath test will be allowed within 48 hours of the first test only at the first Screening Visit (Week -5). The repeat test must be negative for inclusion in the study.
17. Positive urine test for drugs of abuse at the Screening/Qualification Visits (Week -5, -3; see APPENDIX B).

    Note: Patients with a positive urine drug screen for benzodiazepines may be allowed in the study provided the drug was prescribed by a physician as an anxiolytic or sleep aid.

    Note: Use of THC/cannabinoid products is allowed in the study
18. Patients with positive blood screen for human immunodeficiency virus (HIV antibody) and/or hepatitis B virus surface antigen.

    Note: Patients with asymptomatic hepatitis C are allowed as long as the clinical laboratory mentioned above requirements are met.
19. Patients with history of renal disease or those taking medications to treat renal disease.
20. Any other clinically significant medical condition (e.g. fever, active infection, uncontrolled diabetes, cardiovascular conditions including Class III or IV heart failure, pulmonary embolism, deep vein thrombosis, active major autoimmune disease, neurological disease, cancer not in remission for last 3 years except basal cell and squamous cell carcinoma), or procedure as determined by the Investigator, that may unfavorably alter the risk-benefit of study participation, adversely affect study compliance, or confound interpretation of study results.

Criteria for Evaluation

Primary Efficacy Endpoint:

- The primary efficacy endpoint will be the change in PANSS total score at Week 12 from Baseline

***Secondary Efficacy Endpoints*:**

- Change in Clinical Global Impression-Severity (CGI-S) score at Week 12 from Baseline
- Change in Personal and Social Performance (PSP) Scale score at Week 12 from Baseline

***Exploratory Endpoints*:**

- Change in PANSS total score at Weeks 2, 4, 8, and 10 from Baseline
- Change in PANSS Positive Symptoms Factor Score (PSFS) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS Negative Symptoms Factor Score (NSFS) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in CGI-S score at Weeks 2, 4, 6, 8, and 10 from Baseline
- Change in PSP score at Week 6 from Baseline
- Change in Schizophrenia Quality of Life (SQLS) at Week 12 from Baseline

***Safety Measures*:**

- Vital signs, physical examinations, ECGs, clinical laboratory parameters including BUN, serum creatinine and complete urinalysis
- Adverse events
- Extrapyramidal symptoms (EPSs) will be evaluated using the Simpson-Angus Scale (SAS) Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS)
- Assessment of suicidality will be performed using the C-SSRS.

Statistical methods:

Sample size: Approximately 75 patients will be randomized to each treatment arm to achieve a sample size of approximately 60 patients per arm who complete the study. A sample size of 60 per arm provides at least 80% power for the change at Week 12 from Baseline in PANSS total score, assuming a treatment difference from placebo of 5.2 and standard deviation of 10, on a two-sided t-test at 0.05 significance.

Analysis Populations: The Safety Population will include all randomized patients who receive at least one dose of Study Medication. The Efficacy Population will include all patients who receive Study Medication and have at least one post-baseline PANSS assessment during the Treatment Period. The Per Protocol analysis population will include all patients in the Efficacy Population who were dosed according to protocol with no major protocol deviations.

Efficacy Analyses: All statistical tests will be 2-sided with a significance value of 0.05. There will be no adjustments for multiple comparisons to placebo in this Phase 2 study. A mixed effects repeated measures model will be used to assess treatment group differences for change from Baseline. The model will include treatment, analysis visit, treatment-by-visit interaction, the baseline value as a covariate, and patient as a random effect. The comparison of each CTP-692 dose group versus placebo will be assessed by forming the least squares means estimate of each the CTP-692 dose group and comparing it to the placebo group at each post baseline analysis visit. An unstructured covariance structure was used to model the within-patient errors.

Additional details will be summarized in the Statistical Analysis Plan.

Safety Analyses: All safety summaries will be descriptive with no statistical hypothesis testing and will be based on the Safety Population. Adverse events, vital sign measurements, physical examination findings, ECG, clinical laboratory information, concomitant medications, EPSs and C-SSRS will be tabulated and summarized descriptively. Patients will be summarized according to the Study Medication received (i.e., as treated), should it differ from the randomized treatment arm. Adverse events will be coded by system organ class and preferred term with the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant and prior medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or special term	Explanation
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ALB	Albumin
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AP	Antipsychotic
aPTT	Partial Prothrombin Time Test
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration-time curve
BARS	Barnes Akathisia Rating Scale
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity Score
CK	Creatine Kinase
Cl	Chloride
CL/F	Apparent oral clearance
C_{max}	Maximum observed plasma concentration
CO_2	Carbon Dioxide
CogScreen®	Computerized neurocognitive assessment
CPT	Continuous Performance Test
CRA	Clinical Research Associate
CRF	Case Report Form

Abbreviation or special term	Explanation
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation (in percentage)
DMP	Data Management Plan
DSM	Diagnostic and Statistical Manual
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EPS	Extrapyramidal symptoms
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
g	Grams
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HBsAg	Hepatitis B surface Antigen
hCG	Human Chorionic Gonadotropin
HCV-Ab	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
HIV-Ab	Human Immunodeficiency Virus Antibody
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IP	Investigational Product
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation or special term	Explanation
K	Potassium
kg	Kilogram
L	Liter
LDH	Lactic Dehydrogenase
LOCF	Last Observation Carried Forward
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MINI	MINI International Neuropsychiatric Interview
mIU	Milli-International Units
mL	Milliliter
msec	Millisecond
Na	Sodium
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate Receptor
NSFS	Negative Symptoms Factor Score
PANSS	Positive and Negative Symptom Scale
PI	Principal Investigator
PK	Pharmacokinetics
PR	Pulse Rate
PSFS	Positive Symptoms Factor Score
PSP	Personal and Social Performance
PT	Prothrombin Time Test
QD	Taken Daily
QTcF	Fridericia's Corrected QT interval
RR	Respiratory Rate
SAE	Serious Adverse Event
SAS	Simpson-Angus Scale
SANS	Scale for Assessment of Negative Symptoms
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

Abbreviation or special term	Explanation
SQLS	Schizophrenia Quality of Life
SUSARs	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Elimination half-life
T_{max}	Time to observed maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
UACR	Urine Microalbumin/Creatinine Ratio
ULN	Upper Limit of Normal
US	United States
µg	Microgram
WBC	White Blood Cell

4. INTRODUCTION

Schizophrenia is a chronic, complex and debilitating mental disorder associated with high morbidity and mortality. Typical onset of schizophrenia is during late adolescence and early adulthood. The disease is characterized by positive symptoms (hallucinations, delusions, and disorganized thoughts), negative symptoms (flat affect, anhedonia, ambivalence, and amotivation), and cognitive deficits (associated with memory, judgement, and executive planning). Individuals living with schizophrenia report worse health-related quality of life and have significantly reduced life expectancy.

Despite intense ongoing research, the outcomes from best practice treatment are often suboptimal. The median proportion of people with schizophrenia who meet clinical and social recovery criteria is only 13.5% (Charlson, 2018). Antipsychotic drugs that act by blocking dopamine D2 receptors (typical antipsychotics) or both the D2 and serotonin (5-HT_2) receptors (atypical antipsychotics) have been the mainstay of treatment for psychosis and positive symptoms for many years; however, a substantial proportion of patients remain symptomatic (Lane, 2013; Bugarski, 2016) due to lack of efficacy and/or poor tolerability.

N-methyl-D-aspartate receptor (NMDAR) hypofunction is believed to have an important role in the pathophysiology of schizophrenia (Balu, 2015). In patients with schizophrenia, D-serine, an endogenous co-agonist for the NMDA receptor, concentrations in the blood, cerebrospinal fluid (CSF), and in postmortem brain tissue have been reported to be lower than normal controls (Hashimoto, 2003; Hashimoto, 2005; Cho, 2016; Bendikov, 2007). Potentiation of the NMDAR-mediated neurotransmission by glycine site modulators, including D-serine, is considered a novel treatment approach to help improve symptoms of schizophrenia and a number of clinical studies have shown benefit to patients with schizophrenia following treatment with D-serine (Tsai, 1998; Heresco-Levy, 2005; Lane, 2005; Lane, 2010; Kantrowitz, 2010; Ermilov, 2013; Kantrowitz, 2018). A potential limitation to the development of D-serine as a therapeutic is that it has been shown in preclinical testing to cause nephrotoxicity in rats (Ganote, 1974). The cause of nephrotoxicity is believed to result from the production of hydrogen peroxide in the kidney by D-amino acid oxidase (Mothet, 2000; Verrall, 2010).

CTP-692 is a deuterated analog of D-serine and in nonclinical studies has been shown to have nearly identical binding and functional properties as D-serine at the NMDA receptor. In rats, CTP-692 was found to have greater brain exposure when compared to D-serine. Importantly, in other preclinical investigations in the rat, the renal toxicity of D-serine was demonstrated by dose related increases in serum BUN and creatinine but over the same dose range CTP-692 was found to have no significant increase in these parameters, suggesting the potential for an improved renal safety profile for the compound.

The CTP-692 Investigator's Brochure (IB; CTP-692 Investigator's Brochure, Concert Pharmaceuticals Inc., 2019.) should be consulted for detailed technical information and discussion of previous clinical and non-clinical evaluations.

4.1. Summary of D-Serine Clinical Data in Patients with Schizophrenia

One of the first studies to demonstrate that D-serine provided significant beneficial effects on positive, negative and cognitive schizophrenia symptoms when administered as an adjunctive

therapy to stable antipsychotic (AP) regimens was a 6-week double-blind, placebo-controlled trial conducted by Tsai et al (Tsai, 1998). At the end of the 6-week trial, D-serine (30 mg/kg/day) resulted in a 17% reduction in the positive symptoms (Positive and Negative Syndrome Scale [PANSS]-positive subscale, p=0.004) and a 21% reduction of the negative symptoms (Scale for Assessment of Negative Symptoms [SANS], p=0.0004); the placebo group showed a 3% increase in PANSS-positive subscale score and 0.7% reduction in the SANS score. Scores of the PANSS-cognitive subscale also indicated a significant 12% improvement in the D-serine group (p=0.004) compared to 0.8% in the placebo group. In another study with a similar design and dose of D-serine (2 g/day; Lane HY, 2010), the reduction in the PANSS total score in the D-serine group (13%, p = 0.0024) was superior to that observed in the placebo group (4%). Higher doses of D-serine (60 mg/kg and 120 mg/kg) have also been explored and have shown dose-dependent improvements in PANSS total and subscale scores (Kantrowitz, 2010; Kantrowitz, 2018). A study to assess the efficacy of D-serine as an add-on pharmacotherapy to risperidone and olanzapine (Heresco-Levy, 2005) resulted in significant improvements in negative, positive, cognitive and depression symptoms as measured by the PANSS scale.

The majority of studies with D-serine in patients have used a dose of 30 mg/kg/day, a few have administered 60 mg/kg/day and in one study the highest dose was 120 mg/kg/day. The doses of D-serine in these studies approximated to 2.1 g/day, 4.2 g/day and 8.4 g/day, respectively, for a body weight of about 70 kg. The duration of treatment with D-serine ranged from 1 day (single dose) to 4 weeks of daily treatment with the 120 mg/kg/day dose (Kantrowitz, 2010) and 16 weeks of daily treatment with 60 mg/kg/day (Kantrowitz, 2015). D-serine was well tolerated in almost all subjects across all doses. Kantrowitz (2010) dosed 30 mg/kg/day, 60 mg/kg/day and 120 mg/kg/day as 2 divided daily doses of D-serine for 4 weeks with no safety issues at doses < 120 mg/kg. At the 120 mg/kg dose, 1 of 16 patients showed 2+ proteinuria without glycosuria during the final week of treatment with no significant change in creatinine. The proteinuria resolved following D-serine discontinuation, two patients discontinued for asymptomatic transaminitis which also resolved, and two additional patients withdrew consent for side effects (insomnia after one dose and GI distress). In the Kantrowitz (2015) study that dosed 60 mg/kg/day for 16 weeks, two patients in the D-serine group withdrew from the study due to out of range renal values that were possibly related to study treatment versus none in the placebo group. Trace or greater proteinuria was observed in 17 of 45 individuals in post-screening urinalysis. Of these 17 individuals, 11 were randomly assigned to D-serine and 6 were randomly assigned to placebo. All abnormalities resolved during continued treatment. For other adverse events, 1 of 20 patients in the D-serine group expressed suicidal thoughts at Week 11 and was hospitalized but remained in the study. Two patients of 24 in the placebo group were withdrawn from the study due to conversion to psychosis versus none in the D-serine group. However, one patient in the D-serine group showed psychosis symptoms at the final study visit.

The results described above suggest clinical benefit of D-serine in patients with schizophrenia, however, its full clinical potential may be limited due to preclinical nephrotoxic findings at higher, and potentially more clinically-relevant, doses. Given the improved preclinical profile, CTP-692 has the potential to be an adjunctive treatment of schizophrenia with less renal toxicity risk compared to D-serine.

4.2. Summary of CTP-692 Clinical Data

The Phase 1 program was designed to assess the safety, tolerability and pharmacokinetic profile of CTP-692 in healthy volunteers. The Phase 1 program included three studies: a crossover comparison of CTP-692 versus D-serine (CP692.1001), a single-ascending dose study that also assessed the effect of food on the pharmacokinetics of CTP-692 (CP692.1002), and a multiple-ascending dose trial assessing CTP-692 dosed orally over seven days (CP692.1003). The total number of healthy subjects exposed to one or more doses of CTP-692 in the three Phase 1 studies conducted to date is 67. The goals of the early clinical development program for CTP-692 were (1) to characterize the single- and multiple-dose plasma pharmacokinetic (PK) profiles of the drug, (2) to evaluate safety and tolerability of the drug following single- and multiple-dose administration and (3) to provide guidance for dose selection in subsequent efficacy studies in patients with schizophrenia. The CTP-692 IB (CTP-692 Investigator's Brochure, Concert Pharmaceuticals Inc., 2019.) should be consulted for information on CP692.1001. The single-ascending dose study (CP692.1002) and multiple-ascending dose study (CP692.1003) are discussed below.

4.2.1. Study CP692.1002

Study CP692.1002 was a randomized, double-blind, placebo controlled, Phase 1 study in healthy volunteers to characterize the safety, tolerability and plasma PK profile of single ascending oral doses of CTP-692. There were 4 cohorts (Cohort 1: 0.5 g CTP-692, Cohort 3: 2 g CTP-692, Cohort 4: 3 g CTP-692 and Cohort 5: 4 g CTP-692) of 8 subjects each and 1 cohort (Cohort 2:1 g of CTP-692) of 10 subjects. Subjects were randomized 3:1 (CTP-692: placebo) in Cohorts 1, 3, 4 and 5 and 4:1 (CTP-692: placebo) in Cohort 2. A total of 42 healthy volunteers were enrolled in this study (32 received CTP-692; 10 received placebo).

This study involved two Periods: In Period 1, the safety and plasma PK profile of single doses of CTP-692 were evaluated under fasted conditions. In Period 2, the subjects who received 1 g of CTP-692 in Period 1 underwent a 4-day washout (96 hours from Period 1 dose administration) and each subject received the same treatment they received in Period 1 (1 g CTP-692 or placebo) under fed conditions. The caloric content of the meal was in accordance with the FDA guidance for food-effect studies (FDA, 2002). In both periods, CTP-692 was administered orally as a solution formulation.

Plasma pharmacokinetic parameters for CTP-692 are shown in Table 2 below.

Table 2: CP692.1002 Summary of Plasma Pharmacokinetic Parameters

Treatment	Median (range)	Arithmetic Mean (CV%)					
	T_{max} (hr)	C_{max} (µg/mL)	$t_{1/2}$ (hr)	$AUC_{0\text{-}tlast}$ /$AUC_{0\text{-}48hr}$ (hr*µg/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	Vz/F (L)
0.5 g CTP-692 (Fasted, n=6)	1.0 (0.5 – 1.5)	11.0 (26%)	15.9 (9%)	75.1 (13%)	82.2 (13%)	6.17 (13%)	141 (12%)
1 g CTP-692 (Fasted, n=8)	1.0 (0.5 – 1.5)	22.3 (21%)	19.2 (22%)	144 (16%)	164 (18%)	6.28 (17%)	171 (18%)
1 g CTP-692 (Fed, n=8)	2.0 (1.0 – 4.0)	15.3 (30%)	17.9 (17%)	153 (18%)	173 (21%)	5.99 (19%)	152 (15%)
2 g CTP-692 (Fasted, n=6)	1.0 (0.5 – 1.5)	46.3 (20%)	20.2 (22%)	274 (21%)	315 (21%)	6.56 (19%)	191 (25%)
3 g CTP-692 (Fasted, n=6)	1.0 (0.5 – 2.0)	69.1 (41%)	20.6 (9%)	425 (27%)	489 (27%)	6.68 (31%)	196 (33%)
4 g CTP-692 (Fasted, n=6)	1.0 (0.5 – 1.0)	96.5 (19%)	18.4 (15%)	556 (22%)	618 (21%)	6.69 (20%)	179 (27%)

After single oral administration of CTP-692 at dose levels ranging from 0.5 to 4 g in the fasted state, the median T_{max} was 1 hour (range of 0.5 to 2 hours) and the mean $t_{1/2}$ was approximately 19 hours across all 5 dose groups. Increases in the dose level of CTP-692 lead to dose-proportional increases in exposure.

After single oral dose administration of the 1 g CTP-692 in the fed state the T_{max} of CTP-692 was delayed with a median value of 2 hours compared to a median T_{max} of 1 hour in the fasted state. The mean $t_{1/2}$ was similar (18 to 19 hours) in the fed and fasted states. Comparison of the CTP-692 exposure parameters between the fasted and the fed states indicates that food decreases the C_{max} of CTP-692 by about one third, without any effect on AUC.

Overall, CTP-692 was well tolerated in all subjects in this study. The renal function laboratory parameters in blood (serum creatinine and BUN) and urine (complete urinalysis) remained within the normal range at all time points (8, 24 and 48 hours) post-dose in all subjects in the 0.5 g, 1 g, 3 g and 4 g dose groups. In the 2 g dose group only, the serum creatinine levels increased to above the normal range at 8 hours post-dose in 5 out of 6 subjects who received CTP-692 and importantly, in the 2 subjects who received placebo. The creatinine levels returned to the normal range by 24 hours post-dose. On further investigation, it was determined that this finding was attributed to an artifact due to the meals eaten prior to blood draw which included cooked meat. The literature supports the finding of increases in serum creatinine following a diet that includes cooked meat (Mayersohn, 1983; Nair, 2014; Pimenta, 2016). Meal content and timing was controlled for the 3 and 4 g dose cohorts and no such increase in creatinine was observed, supporting the belief

that the 2 g cohort findings were artefactual. CTP-692- and Placebo-related adverse events were mild-moderate in severity and were reported in a total of 6 and 2 subjects, respectively (see Table 3 below).

Table 3: CP692.1002 Adverse Events

Adverse Event	Number of Events					
	Placebo	0.5 g CTP-692	1 g CTP-692	2 g CTP-692	3 g CTP-692	4 g CTP-692
Number of Subjects: AE/Total	2/10	1/6	3/8	1/6	1/6	0/6
Headache	1	1	2	1	1	0
Nightmares	0	0	1	0	0	0
Fogginess, metallic taste, irritability	0	0	0	1	0	0
Abdominal pain, nausea, vomiting	0	0	0	0	1	0
Tiredness	1	0	0	0	0	0
Mental fogginess	1	0	0	0	0	0

All adverse events resolved/recovered by the end of the study. There were other no other clinically significant safety-related findings including clinical laboratory tests, vital signs, and ECG assessments.

Exploratory assessments included an assessment of neurocognitive effects using computerized testing (CogScreen®). The CogScreen test battery included tests of digit symbol substitution (processing speed), previous number recall (working memory), verbal working memory, executive functioning, reaction time, and vigilance. Results showed no evidence of adverse effects on neurocognitive functioning at any of the 5 doses.

4.2.2. Study CP692.1003

Study CP692.1003 was a randomized, double-blind, placebo-controlled study in healthy volunteers to characterize the safety, tolerability and plasma PK profile of 3 ascending dose levels of CTP-692 following once-daily oral administration for 7 consecutive days. There were 3 cohorts (Cohort 1: 1 g CTP-692, Cohort 2: 2 g CTP-692, Cohort 3: 4 g CTP-692) of up to 10 subjects (8 active and 2 placebo) in each cohort. A total of 30 healthy volunteers were enrolled in this study (24 received CTP-692; 6 received placebo). Based on the results of the food effect observed (reduced C_{max} and the similar AUC) in the single dose study (CP692.1002), CTP-692 was administered orally as a solution formulation within approximately 1 hour of consumption of food in this study.

Preliminary plasma pharmacokinetic parameters for CTP-692 are shown in Table 4 below.

Table 4: CP692.1003 Summary of Plasma Pharmacokinetic Parameters

Treatment	Day	T_{max} (hr)	C_{max} (µg/mL)	$t_{1/2}$ (hr)	AUC_{tau} /$AUC_{0\text{-}24hr}$ (µg*hr/mL)	AUC_{inf} (µg*hr/mL)
1 g CTP-692 (n=8)	1	1.5 (1.0 – 3.0)	22.2 (14%)	Not reported	136.4 (14%)	162.6 (12%)
	7	1.5 (0.5 – 3.0)	25.3 (12%)	21.1 (18%)	175.3 (23%)	263.2 (30%)
2 g CTP-692 (n=8)	1	1.0 (1.0 – 2.0)	47.9 (23%)	Not reported	258.6 (13%)	330.7 (23%)
	7	1.0 (0.25 – 2.0)	52.0 (23%)	21.3 (23%)	332.6 (11%)	522.0 (19%)
4 g CTP-692 (n=8)	1	1.5 (1.0 – 2.0)	68.9 (30%)	Not reported	393.5 (11%)	566.1 (24%)
	7	2.0 (1.0 – 4.0)	70.8 (26%)	24.4 (29%)	539.1 (14%)	911.4 (19%)

After oral administration of CTP-692 at dose levels of 1, 2 and 4 g for 7 consecutive days, the median T_{max} on Day 7 ranged from 1 to 2 hours and the mean $t_{1/2}$ on Day 7 ranged from 21–24 hours across the 3 doses. CTP-692 plasma concentrations reached steady-state by approximately Day 5. On Day 7, increases in the dose of CTP-692 lead to dose-proportional increases in C_{max} and AUC_{tau} for the 2 g dose relative to the 1 g dose; however, the increase for the 4 g dose was less-than dose proportional. The increase in AUC_{inf} was approximately dose-proportional across the 3 doses on Day 7. The C_{max} accumulation on Day 7 was approximately 14%, 9% and 3% for the 1, 2 and 4 g doses, respectively. The AUC_{tau} accumulation on Day 7 was approximately 28% for the 1 and 2 g doses, and 37% for the 4 g dose.

CTP-692 was well tolerated in all subjects in this study. The renal function laboratory parameters in blood (serum creatinine and BUN) and urine (complete urinalysis) remained within the normal range at all time points (24 hours post-dose administration on each day) in all subjects in all 3 dose groups.

CTP-692- and Placebo-related adverse events were mild-moderate in severity and were reported in a total of 7 subjects and 1 subject, respectively (see Table 5 below).

Table 5: CP692.1003 Adverse Events

Adverse Event	Number of Events			
	Placebo	1 g CTP-692	2 g CTP-692	4 g CTP-692
Number of Subjects: AE/Total	1/6	5/8	2/8	0/8
Headache	0	3	2	0
Eructation, gastric upset	0	1	0	0
Dry mouth	0	1	0	0
Sleepiness/drowsiness	0	1	1	0
Loose stool	1	0	0	0

All adverse events resolved/recovered by the end of the study. There were no adverse events reported in the 4 g cohort. There were no other clinically significant safety-related findings including clinical laboratory tests, vital signs, and ECG assessments.

5. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312, and the International Council for Harmonization (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki and applicable local regulatory requirements and law.

The Investigator is responsible for protecting the rights, safety, and welfare of patients under his/her care, and for the control of the medications under investigation. All ethical, regulatory, and legal requirements must be met before the first patient is enrolled in the study.

5.1. Institutional Review Board (IRB)

The Institutional Review Board (IRB) will meet all FDA requirements governing IRBs according to CFR, Title 21, Part 56. The Investigator (or designee) must submit this study protocol and any amendments, the Sponsor's approved informed consent form(s) (ICF), patient information sheets, patient recruitment materials, and other appropriate documents to the IRB for review and approval. Following review of the submitted materials a copy of the written and dated approval/favorable opinion will be forwarded to the Sponsor (or designee).

Any advertisements used to recruit patients for the study will be reviewed by the Sponsor and the IRB prior to use.

5.2. Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the patient.

The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50. The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary must be explained to the patient. The patient must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's source documentation prior to any testing under this protocol, including screening tests and assessments. The original signed consent form will be retained with the study records.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the and the Sponsor and relevant IRB.

6. STUDY OBJECTIVES

The objectives of this study are to evaluate the efficacy and safety of CTP-692 as an adjunctive treatment in adult patients with schizophrenia. The efficacy and safety measures are:

Primary Efficacy Endpoints:

- The primary efficacy endpoint will be the change in PANSS total score at Week 12 from Baseline

***Secondary Efficacy Endpoints*:**

- Change in Clinical Global Impression-Severity (CGI-S) score at Week 12 from Baseline
- Change in Personal and Social Performance (PSP) Scale score at Week 12 from Baseline

***Exploratory Endpoints*:**

- Change in PANSS total score at Weeks 2, 4, 8, and 10 from Baseline
- Change in PANSS Positive Symptoms Factor Score (PSFS) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS Negative Symptoms Factor Score (NSFS) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in CGI-S score at Weeks 2, 4, 6, 8, and 10 from Baseline
- Change in PSP score at Week 6 from Baseline
- Change in Schizophrenia Quality of Life (SQLS) at Week 12 from Baseline

***Safety Measures*:**

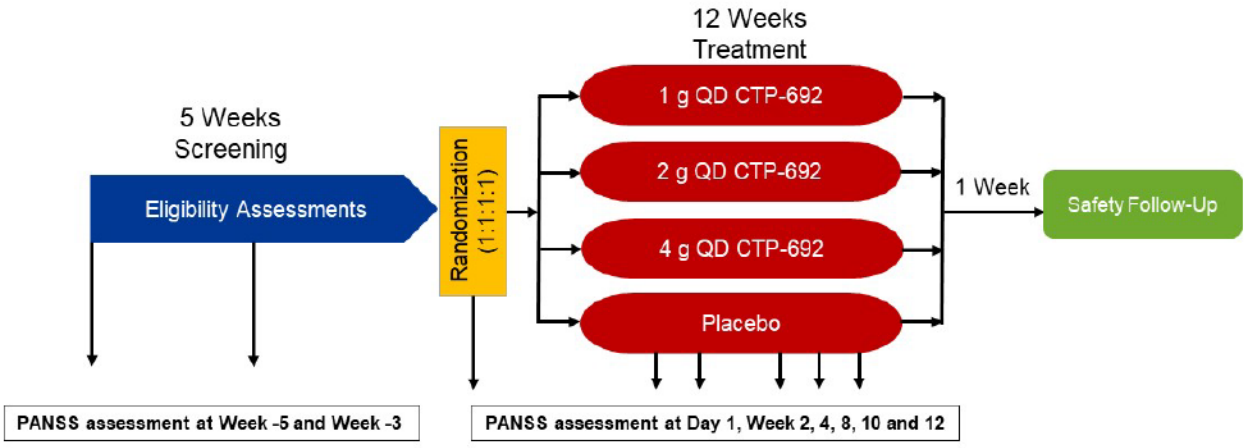
- Vital signs, physical examinations, electrocardiograms (ECGs), clinical laboratory parameters including blood urea nitrogen (BUN), serum creatinine and complete urinalysis
- Adverse events
- Extrapyramidal symptoms (EPSs) will be evaluated using the Simpson-Angus Scale (SAS) Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS)
- Assessment of suicidality will be performed using the Columbia-Suicide Severity Rating Scale (C-SSRS)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel group, placebo-controlled, multicenter study. At screening, potential study participants must have a DSM-V diagnosis of schizophrenia for at least 2 years and confirmed by psychiatric evaluation and MINI. The study will involve patient participation for up to 20 weeks and will consist of a 5-week Screening/Qualification Period, a 12-week Treatment Period and a Safety Follow-Up Visit approximately 1 week after the last dose of Study Medication. The Qualification period may be extended up to 2 weeks (after Week -3, prior to Randomization) if repeat laboratory test results for confirmation of eligibility are pending. Approximately 300 patients, 18-55 years old, will be randomized to receive 1 g, 2 g or 4 g of CTP-692 or Placebo once-daily (QD). At the first Screening Visit (Week -5), patients will provide informed consent and will be assessed for eligibility based on study inclusion and exclusion criteria, including a total score of 70-110 on the Positive and Negative Syndrome Scale (PANSS). Patients meeting eligibility requirements at the first Screening Visit will undergo an additional in-clinic Qualification Visit (at Week -3). Patients who continue to meet eligibility criteria based on assessments at the Screening and Qualification visits and Day 1 will be randomized in a 1:1:1:1 ratio to 1 of the 4 treatment groups shown below in Figure 1:

Figure 1: CP692.2001 Study Design



Note: The Qualification period may be extended up to 2 weeks (after Week -3, prior to Randomization) if repeat laboratory test results for confirmation of eligibility are pending.

Patients will receive their first dose of Study Medication in the clinic on Day 1. The dose of CTP-692 or Placebo should be administered with food. Patients will be instructed to take Study Medication once daily at home with food in the morning for the next 12 weeks. Patients will return to the clinic at Weeks 2, 4, 6, 8, 10, and 12 for safety and efficacy assessments and to pick up Study Medication as shown in Table 6. Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, clinical laboratory blood draws may be performed by a Home Health Care service provider or by a local laboratory; other safety and efficacy assessments may be performed remotely via phone/audio or video conferencing platforms (with the exception of Facebook). Study personnel should strive to perform assessments within the visit window as shown in Table 6 with the understanding that not all assessments may be able to

be performed. Missed assessments will be recorded in the eCRF with notation that the missed assessment was due to the COVID-19 pandemic.

Phone contact will be made with the patient on Weeks 1, 3, 5, 7, 9 and 11. Patients may be requested to make Unscheduled Visits to the clinic if the Investigator (or designee) thinks necessary.

The primary outcome measure will be the change in PANSS total score at Week 12 from Baseline. Patients will be required to return to the clinic approximately 1 week after the last dose of Study Medication for safety assessments including physical examination, adverse-events and concomitant medications as shown in Table 6. Due to the COVID-19 pandemic the Safety Follow-up visit may be conducted remotely via phone/audio or video conferencing platforms (with the exception of Facebook) per Investigator discretion. If any of the safety parameters including clinical laboratory parameters at the end of the Treatment Period are reported to be abnormal, unscheduled assessments may be performed at the Safety Follow-Up Visit and additional follow-up may be required as the Investigators deem necessary. Patients who experience intolerable symptoms during the Treatment Period may discontinue the study at the discretion of the Investigator.

7.2. Rationale for CTP-692 Dose Selection

The clinical benefit of D-serine in patients with schizophrenia has been described in the literature using a dose range of approximately 2 g to 8 g per day (assuming 70 kg subjects). Given its preclinical profile, CTP-692 has the potential to have an improved renal safety profile and have substantially better brain exposure compared to D-serine. Consequently, the top dose of CTP-692 chosen for the Phase 1 single- and multiple-ascending dose studies was 4 g (see Section 4.2). The doses for this Phase 2 study were selected based on the safety, tolerability and pharmacokinetic profile of CTP-692 in the Phase 1 studies. The 1 g, 2 g and 4 g doses of CTP-692 from the Phase 1 studies were chosen as they were well tolerated in healthy volunteers with no renal laboratory parameter abnormalities and no other clinically significant safety-related findings. In the single-dose studies (CP692.1001 and CP692.1002), there were only a few CTP-692-related mild-moderate adverse events reported of which headache was the most common. The multiple-dose study (CP692.1003) also reported few treatment-related mild-moderate adverse events with headache being most common. The pharmacokinetic profile of CTP-692 supports once-daily dosing with modest AUC accumulation following 7 consecutive days of administration of all three doses.

7.3. Number of Patients

Approximately 75 patients will be randomized to each treatment arm to achieve a sample size of approximately 60 patients per arm who complete the study. A total of approximately 300 patients will be enrolled in this study.

7.4. Criteria for Study Termination

There are no prospective stopping criteria for this study. The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

Any termination required by the Sponsor must be implemented by the Investigator, if instructed to do so, in a time frame that is compatible with the patient's well-being.

8. STUDY PROCEDURES

8.1. Schedule of Assessments

The schedule of study procedures is provided in Table 6.

Table 6: Schedule of Assessments

	Screening	Qualification[1]	Treatment Period[9]													Safety Follow-Up[12]
Week	-5	-3	0	1	2	3	4	5	6	7	8	9	10	11	12[3]	13
Day	-35	-24 to -21	1[2]													
Informed consent	X															
Eligibility	X	X	X													
Demographics	X															
Medical history	X		X													
Serology, FSH[4]	X															
MINI	X															
Randomization			X													
Dispense Study Medication[10]			X		X		X		X		X		X			
Study Medication accountability					X		X		X		X		X		X	
Full physical exam	X		X												X	
Brief physical exam					X		X		X		X		X			X
Height	X															
Weight	X		X		X		X		X		X		X		X	
BP, PR, RR, Temperature	X		X		X		X		X		X		X		X	
12-lead ECG[11]	X		X						X						X	
Urine pregnancy test[5]	X		X		X		X		X		X		X		X	
Hematology, serum chemistry, coagulation[6]	X		X						X						X	
Serum renal parameters and urinalysis[6]	X		X		X		X		X		X		X		X	
Urine drug test	X	X														
Alcohol breath test	X	X	X		X		X		X		X		X		X	
PANSS	X	X	X		X		X				X		X		X	
PSP Scale			X						X						X	
CGI-S			X		X		X		X		X		X		X	
SQLS			X												X	
C-SSRS	X	X	X		X		X		X		X		X		X	
SAS, AIMS, BARS			X						X						X	

	Screening	Qualification[1]	Treatment Period[9]												Safety Follow-Up[10]
Week	-5	-3	0	1	2	3	4	5	6	7	8	9	10	11	12[3]	13
Day	-35	-24 to -21	1[2]													
AP blood sample		X														
CTP-692 blood sample[7]					X		X		X		X		X		X	
Genetic testing blood sample[8]			X													
Phone Call Check-in				X		X		X		X		X		X		
Adverse events	X	X	X (Continuous)													
Concomitant medications	X	X	X (Continuous)													

AP = antipsychotic, AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, BP = blood pressure, CGI-S = Clinical Global Impression-Severity, C-SSRS = Columbia-Suicide Severity Rating Scale, EPS = Extra-pyramidal Symptoms, MINI = MINI International Neuropsychiatric Interview, PANSS = Positive and Negative Symptom Scale, PR = Pulse Rate, PSP = Personal and Social Performance, RR = Respiratory Rate, SAS = Simpson-Angus Scale, SQLS = Schizophrenia Quality of Life

[1] The Qualification period may be extended up to 2 weeks if repeat laboratory test results for confirmation of eligibility are pending.
[2] All subsequent visits and weeks should be based on the date of Day 1. All post-Day 1 visit windows are ±2 days.
[3] Patients who withdraw/discontinue from the study early should have all Week 12 assessments performed.
[4] FSH test for post-menopausal women only.
[5] Pregnancy test for females of childbearing potential only.
[6] Blood and urine samples should be drawn/collected prior to dose of Study Medication when dose is administered in the clinic.
[7] CTP-692 blood samples should be taken pre-dose at Weeks 2, 4, 6, 8, and 10 when dose is administered in the clinic, and post-dose at Week 12.
[8] Patients must sign the optional genetic blood sample genetic research consent form.
[9] Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, clinical laboratory blood draws may be performed by a Home Health Care service provider or by a local laboratory; other safety and efficacy assessments may be performed remotely via phone/audio or video conferencing platforms (with the exception of Facebook).
[10] When study assessments are not conducted in the clinic due to the COVID-19 pandemic, the Study Medication may be sent directly to the patient.
[11] Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, if Week 6 is a remote visit, ECG assessment may be performed at Week 8 or Week 10.
[12] Due to the COVID-19 pandemic, the Safety Follow-up may be conducted remotely per Investigator discretion.

8.2. Study Procedures

8.2.1 Screening Period Procedures (Week -5 and Week -3)

Prior to performing any study-related activities or evaluations, the patient must be thoroughly informed about all aspects of the study, including scheduled visits and activities. Patients will sign the study-specific consent form(s) prior to any screening procedure. Patients will be instructed to report all AEs that occur during the study from the time of informed consent forward.

Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, some Screening Period procedures (with the exception of PANSS) such as the MINI, medical history, review of concomitant medications) may be conducted remotely per Investigator discretion. The consent process must be conducted in the clinic and patients must sign the ICF in person in the clinic.

Patients should continue to take their prescribed AP medication throughout the Screening and Treatment Periods.

The following procedures will be performed at **Week -5:**

- Assessment of eligibility according to inclusion/exclusion criteria
- Conduct psychiatric evaluation and administer MINI International Neuropsychiatric Interview Psychotic Disorders, version 7.0.2 (MINI, Version 7.0.2; see APPENDIX L)
- Demographics, medical history, including query for baseline signs/symptoms (ie, an AE with onset prior to dosing is to be recorded as a pretreatment AE)
- Review of concomitant medications including stable background AP therapy
- Full physical examination plus height and weight
- Vital signs including blood pressure, pulse rate, respiratory rate, and temperature
- Standard 12-lead ECG
- Urine pregnancy tests for women of childbearing potential
- Alcohol breath test
  - *A repeat alcohol breath test will be allowed within 48 hours of the first test. If the repeat test is positive, the patient must be excluded from the study*
- PANSS
- Assessment of suicidal ideation using C-SSRS (Baseline/Screening version)
- Serology, FSH, serum chemistry, hematology, and coagulation parameter evaluations
- Serum renal parameters and urinalysis

- Urine drug test
  - *Patients with a positive urine drug screen for benzodiazepines may be allowed in the study provided the drug was prescribed by a physician as an anxiolytic or sleep aid*
  - *Use of THC/cannabinoid products is allowed in the study*

The following procedures will be performed at **Week -3**:

- Continue to assess eligibility and review adverse events and concomitant medications including stable background AP therapy
- Urine drug test
  - *Patients with a positive urine drug screen for benzodiazepines may be allowed in the study provided the drug was prescribed by a physician as an anxiolytic or sleep aid*
  - *Use of THC/cannabinoid products is allowed in the study*
- Alcohol breath test
  - *Alcohol breath test must be negative for the patient to continue in the study*
- PANSS
- C-SSRS (Since Last Visit version)
- Blood sample for assessment of prescribed AP levels
  - *Sponsor or designee will provide confirmation of eligibility based on AP blood level*
- The Qualification period may be extended up to 2 weeks if repeat laboratory test results for confirmation of eligibility are pending

8.2.2 Treatment Period Procedures (Day 1 to Week 12)

The following procedures will be performed at **Day 1**:

- Continue to assess eligibility
- Following confirmation of eligibility, consenting patients will be randomized to 1 of the 4 Study Medication groups. The following procedures must be performed prior to administration of Study Medication:
  - Review of adverse events and concomitant medications including stable background AP therapy
  - Full physical examination plus and weight
  - Vital signs including blood pressure, pulse rate, respiratory rate, and temperature
  - Standard 12-lead ECG

  - Urine pregnancy tests for women of childbearing potential
  - Alcohol breath test
    - *Alcohol breath test must be negative for the patient to be randomized to receive Study Medication*
  - Serum chemistry, hematology, and coagulation parameter evaluations
  - Serum renal parameters and urinalysis
  - PANSS, PSP, CGI-S, SQLS
  - C-SSRS (Since Last Visit version)
  - SAS, AIMS, BARS
  - Blood sample for genetic testing (if consent has been given)
- Administration of first dose of Study Medication in the clinic with food
- Dispensation of Study Medication to take home
  - *A 2-week supply of the Study Medication will be provided*

The following procedures will be performed at **Week 2 through Week 12:**

- Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, clinical laboratory blood draws may be performed by a Home Health Care service provider or by a local laboratory; other safety and efficacy assessments may be performed remotely via phone/audio or video conferencing platforms (with the exception of Facebook). Study personnel should strive to perform assessments within the visit window as shown in Table 6 with the understanding that not all assessments may be able to be performed. Missed assessments will be recorded in the eCRF with notation that the missed assessment was due to the COVID-19 pandemic.
- The following procedures must be performed prior to administration of Study Medication:
  - Review of adverse events and concomitant medications including stable background AP therapy
  - Brief physical examination plus weight; vital signs including blood pressure, pulse rate, respiratory rate, and temperature (Weeks 2, 4, 6, 8, 10)
  - Full physical examination plus weight
  - Vital signs including blood pressure, pulse rate, respiratory rate, and temperature (Week 12)

  - Standard 12-lead ECG (Weeks 6 and 12 only; if Week 6 visit is a remote visit, ECG assessment may be performed at Week 8 or 10)
  - Urine pregnancy tests for women of childbearing potential
  - Alcohol breath test
    - *Patient may be discontinued if they test positive at any two visits during the treatment period*
  - Serum chemistry, hematology, and coagulation parameter evaluations (Weeks 6 and 12 only)
  - Serum renal parameters and urinalysis
  - Blood sample for assessment of CTP-692 levels (pre-dose if dose of Study Medication is administered in the clinic at Weeks 2, 4, 6, 8, and 10)
    - *If possible, time of last dose taken should also be recorded*
- Dispensation of Study Medication to take home
  - *A 2-week supply of the Study Medication will be provided at each visit except Week 12*
  - *When study assessments are not conducted in the clinic due to the COVID-19 pandemic, the Study Medication may be sent directly to the patient*
- PANSS (Weeks 2, 4, 8, 10, and 12)
- CGI-S (Weeks 2, 4, 6, 8, 10, and 12)
- C-SSRS (Since Last Visit version)
- PSP (Weeks 6 and Week 12 only)
- SQLS (Week 12 only)
- SAS, AIMS and BARS (Weeks 6 and Week 12 only)
- Blood sample for assessment of CTP-692 levels (post-dose; Week 12 only)
  - *Blood sample should be taken at the end of the visit*
  - *Time of CTP-692 dose and blood draw should be recorded*
- Administration of dose of Study Medication in the clinic with food *at the Week 12 visit*
  - Post Dose blood sample for assessment of CTP-692 levels (Week 12 only)
    - *Blood sample should be taken at the end of the visit*
    - *Time of CTP-692 dose and blood draw should be recorded*

8.2.2.1 Phone Call Check-In (Weeks 1, 3, 5, 7, 9 and 11)

- Patients will receive a phone call 7±2 days after each in-clinic visit (except after Week 12) to discuss any possible adverse events or other medical changes that may have occurred since their last visit
- Patients will also be asked about compliance to AP and Study Medication schedule

8.2.3 Safety Follow-Up Procedures (Week 13)

- Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, the Safety Follow-up visit may be conducted remotely via phone/audio or video conferencing platforms (with the exception of Facebook) per Investigator discretion.
  - Review of adverse events and concomitant medications including stable background AP therapy
  - Brief physical examination (if in-clinic visit)

9. SELECTION AND WITHDRAWAL OF PATIENTS

9.1. Inclusion Criteria

1. Patient should be able to read, understand and voluntarily sign an informed consent document prior to any study related assessments and procedures being conducted. Patients should be willing to comply with the study visits and requirements of the study protocol.
2. Patient should be between 18 and 55 years of age, inclusive, at the time of signing the informed consent document.
3. Physician confirmed DSM-V diagnosis of schizophrenia for the past 2 years based on patient's history and confirmed by psychiatric evaluation and MINI International Neuropsychiatric Interview Psychotic Disorders, version 7.0.2 (MINI, Version 7.0.2; see APPENDIX L).
4. The patient is an outpatient with no hospitalization for worsening of schizophrenia within 3 months of the first Screening Visit (Week -5).
5. Patients currently treated with one antipsychotic (AP) medication which has been unchanged (medication and dose) for at least 7 weeks prior to the first Screening Visit (Week -5), and expected to remain unchanged during the Screening and Treatment period. Allowed orally dosed APs are:

   a. Aripiprazole
   b. Asenapine
   c. Brexipiprazole
   d. Cariprazine
   e. Lurasidone
   f. Olanzapine
   g. Paliperidone
   h. Quetiapine
   i. Risperidone

   Note: If the patient is being treated with depot or long-acting antipsychotics, they should be on the treatment for at least 2 drug administration cycles prior to the first Screening Visit (Week -5).
6. Patients with confirmed blood levels of their current AP medication in samples drawn at the Qualification Visit (Week -3).
7. The patient has a reliable informant who is able to provide information regarding the patient and support study participation.

8. Patients with clinically stable schizophrenia with residual symptoms defined as PANSS total score of 70-110 per evaluation at the first Screening Visit (Week -5), the Qualification Visit (Week -3) and Day 1.

   Note: At Week -3 and Day 1, the PANSS total score may vary by 10 points as compared to a previous visit, as long as total score remains between 70-110 at each of the three visits for the patient to be included in the study.

   Patients must also meet these additional PANSS criteria:

   a. PANSS score of ≤ 4 on positive scale items of conceptual disorganization and hostility
   b. PANSS score ≥ 4 on **at least <u>two</u>** of the following items:
   a. Delusions
   b. Hallucinations
   c. Suspiciousness/Persecution
   d. Unusual thought content

   c. PANSS Negative Symptom Factor Score (NSFS) ≥ 12

9. If of reproductive age and not infertile (defined below), willing and able to use a medically highly effective form of birth control during the study and for 4 weeks following last dose of Study Medication. Examples of medically highly effective forms of birth control are:

   a. Surgical sterility (via vasectomy, hysterectomy or bilateral ligation) or post-menopausal females (have had spontaneous amenorrhea for at least the last 1 year and at least 1 year after the onset of amenorrhea while not receiving hormone replacement therapy and have a Follicle-Stimulating Hormone (FSH) level greater than 40 mIU/mL)
   b. Sexual partner is sterile, or of the same sex
   c. Implants of levonorgestrel in females
   d. Oral contraceptive (combined or progesterone only) in females
   e. Double-barrier method (any combination of physical and chemical methods)
   f. Intrauterine device in females, or other method with published data showing that the lowest expected failure rate is less than 1% per year

10. Healthy, as determined by the Investigator, based on a medical evaluation including history, physical examination, vital signs, electrocardiogram (ECGs) and clinical laboratory assessments at Week -5.

    Note: A patient with a non-clinically significant abnormality or laboratory parameters outside the reference range may be included only if the Investigator considers that the finding will not compromise the patient's safety and will not interfere with the study procedures or data interpretation.

11. Body mass index (BMI) within the range of 18 to 40 kg/m^2, inclusive, at the first Screening Visit (Week -5).

9.2. Exclusion Criteria

1. Patients with DSM-V criteria at the first Screening Visit (Week -5) for disorders other than schizophrenia that in the opinion of the Investigator may interfere with study conduct and interpretation of results.
2. Patients who, in the opinion of the Investigator, have a history of antipsychotic treatment resistance.
3. Patients currently taking clozapine.
4. Patients who have been previously treated with or are receiving electroconvulsive therapy (ECT).
5. Patients who have initiated or changed dose of antidepressants or other moods stabilizers within 7 weeks prior to the first Screening Visit (Week -5).
6. Patients currently taking lithium.
7. Patients taking an AP (e.g. Seroquel) as a sleep aid.

Note: Patients will be allowed to switch to a non-AP sleep aid during the Screening period.

8. Patients who use prescription medications (stimulants) to treat attention deficit hyperactivity disorder or attention deficit disorder.
9. Screening laboratory measurements outside the normal range associated with potential risk for the treatment under investigation at the first Screening Visit (Week -5). This will include but not limited to:
    a. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or total bilirubin > 2x upper limit of normal (ULN)
    b. Estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m^2
    c. Serum creatinine and/or blood urea nitrogen (BUN) > ULN
    d. Urinalysis positive for protein or urine microalbumin/creatinine ratio (UACR) > 30 mg/g

Note: These laboratory tests may be repeated once, if they are abnormal on first screening, and if there is a medical/analytical reason to believe the results may be inaccurate. If the repeat test is within the reference range, the patient may be included only if the Investigator considers that the previous finding will not compromise the patient's safety and will not interfere with the interpretation of safety data.

10. Patients with suicidal behavior occurring within the past year or who pose a current suicide risk as determined by the PI or as confirmed at the first Screening Visit (Week -5), the Qualification Visit (Week -3) or Day -1 by affirmative answer on items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS).
11. Treatment with an investigational drug within 7 weeks or 5 half-lives (if known), whichever is longer, prior to the first Screening Visit (Week -5).
12. Donation of blood within 4 weeks of Day 1.
13. History of prolonged QT syndrome or a Screening QTc interval with Fridericia's correction (QTcF) > 450 msec for males or QTcF > 470 msec for females.
14. Females who are nursing, pregnant, or planning to become pregnant while in the study and for 4 weeks after the last dose of study medication.
15. History of meeting DSM-5 criteria for moderate to severe alcohol or substance use disorder (other than nicotine or caffeine) within the 6 months before the first Screening Visit (Week -5).
16. Positive alcohol breath test.

Note: A repeat alcohol breath test will be allowed within 48 hours of the first test only at the first Screening Visit (Week -5). The repeat test must be negative for inclusion in the study.

17. Positive urine test for drugs of abuse at the Screening/Qualification Visit (Week -5, -3; see APPENDIX B).

Note: Patients with a positive urine drug screen for benzodiazepines may be allowed in the study provided the drug was prescribed by a physician as an anxiolytic or sleep aid

Note: Use of THC/cannabinoid products is allowed in the study

18. Patients with positive blood screen for human immunodeficiency virus (HIV antibody) and/or hepatitis B virus surface antigen.

Note: Patients with asymptomatic hepatitis C are allowed as long as the clinical laboratory mentioned above requirements are met.

19. Patients with history of renal disease or those taking medications to treat renal disease.
20. Any other clinically significant medical condition (e.g. fever, active infection, uncontrolled diabetes, cardiovascular conditions including Class III or IV heart failure, pulmonary embolism, deep vein thrombosis, active major autoimmune disease, neurological disease, cancer not in remission for last 3 years except basal cell and squamous cell carcinoma), or procedure as determined by the Investigator, that may unfavorably alter the risk-benefit of study participation, adversely affect study compliance, or confound interpretation of study results.

9.3. Patient Withdrawal Criteria

Patients may withdraw from participation in the study at any time. The Investigator may withdraw a patient at any time if they believe the safety of the patient or the integrity of the data are at risk. In addition, patients should be withdrawn if they:

- Experience a serious or intolerable AE
- Develop a clinically significant laboratory or ECG abnormality
- Develop proteinuria of 1-2+ or UACR > 30 mg/g as confirmed by a repeat lab test
- Develop eGFR levels < 60 mL/minute/1.73 m^2 as confirmed by a repeat lab test
- Develop *symptomatic* ALT or AST elevation ≥ 2x the ULN on two repeat lab tests or develop *asymptomatic* ALT or AST elevation ≥ 3x the ULN as confirmed by a repeat lab test
- Develop total bilirubin ≥ 2x the ULN as confirmed by a repeat lab test
- Exhibit suicidal behavior as determined by an affirmative answer on items 4 or 5 on the C-SSRS
- Do not follow guidelines specified in the protocol (i.e., is noncompliant with protocol procedures or Study Medication administration) or specific instructions by the study staff
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator
- Are lost to follow up

In case of two consecutive missed safety assessments due to the COVID-19 pandemic, continued patient participation in the study must be discussed by the Investigator and the Medical Monitor.

9.3.1. Patient Withdrawal Procedures

A patient who prematurely discontinues Study Medication/study participation should have all Week 12 assessments performed as an Early Termination Visit, and if possible, return for the Safety Follow-up Visit. In light of the COVID-19 pandemic, study personnel should strive to perform assessments per Table 6 with the understanding that not all assessments may be able to be performed. All missed assessments will be documented in the eCRF with notation that the missed assessment was due to the COVID-19 pandemic. The Safety Follow-Up Visit may be waived by the Sponsor in instances where patients have discontinued dosing prior to the Early Termination Visit on a case-by-case basis.

If a patient terminates early from the study, the Investigator will record the reason(s) for early termination on the relevant electronic case report form (eCRF). The specific reason for the withdrawal should be carefully documented on the eCRF.

Adverse events resulting in patient early termination will be followed to the satisfactory resolution and determination of outcome, as ascertained by the Investigator (and/or Sponsor, or its designee); (See Section 12). The data will be recorded on the appropriate eCRF.

10. DESCRIPTION OF STUDY MEDICATIONS

10.1. Description of Study Medication

Patients meeting eligibility criteria will be randomized in a 1:1:1:1 ratio to one of the following 4 treatment arms:

- Double-blinded CTP-692, 1 g QD for 12 weeks
- Double-blinded CTP-692, 2 g QD for 12 weeks
- Double-blinded CTP-692, 4 g QD for 12 weeks
- Double-blinded Placebo, QD for 12 weeks

Patients will take the first dose of Study Medication in the clinic on Day 1 of the Treatment Period, after the Baseline assessments have been performed and with food. Patients will be instructed to continue taking their Study Medication once daily with food, for a total of 12 weeks. On clinic visit days, when patients take their dose of Study Medication in the clinic, the dose should be administered after the clinical laboratory blood draws and urine collection are completed. If clinical laboratory blood draws and urine collection are performed by a Home Health Care service provider or by a local laboratory, patients should try to take their Study Medication per their normal schedule.

10.2. Treatment Compliance

At each scheduled study visit after randomization, the Investigator or designee will interview the patient regarding treatment compliance and compare the number of dispensed versus returned Study Medication pouches. When study assessments are not conducted in the clinic due to the COVID-19 pandemic, treatment compliance may be assessed via phone/audio or video conferencing platforms or by the Home Health Care service provider. The used and unused Study Medication pouches may be sent back to the site or the patient may save the used and unused pouches and bring back to the next in-clinic visit. Patients should strive for 100% compliance with the daily dosing schedule. Retraining on treatment compliance should occur for patients with less than 80% compliance at any visit and the Sponsor should be notified.

10.3. Study Medication Materials and Management

A complete description of the Study Medication and requirements for storage, handling, dispensing, accountability, returns and destruction can be found in the Pharmacy Manual.

10.3.1. Physical Description of Study Medication

Study Medication will be CTP-692 or matching Placebo. Details regarding formulation and dosage are shown in Table 7.

Table 7: Investigational Product

	Investigational Product
Product Name:	CTP-692 or Matching Placebo
Dosage Form:	Powder for oral solution
Unit Dose	1 g, 2 g or 4 g CTP-692 or Placebo
Route of Administration	Oral
Physical Description	White to off-white powder in a foil pouch
Manufacturer	Sharp Clinical Services, Inc.

10.3.2. Study Medication Packaging, Labelling and Storage

CTP-692 and Placebo will be packaged in foil pouches and labeled by an appropriately qualified vendor. Starting at Day 1 and at each scheduled in-clinic visit, each patient will receive 2 kits containing doses for 2 weeks. When study assessments are not conducted in the clinic due to the COVID-19 pandemic, the Study Medication will be sent directly to the patient.

Details of the packaging, labeling and dispensing instructions can be found in the Pharmacy Manual.

Study Medication should be stored at the clinic in the original package between 15°C to 25°C (59°F to 77°F), as stated on the product label, in a secure, temperature-monitored, locked area, under the responsibility of the Investigator or other authorized individual until dispensed to the patients.

Patients should be advised to store their Study Medication in the original package at room temperature as stated on the package label. No special handling procedures are required.

10.3.3. Study Medication Preparation and Administration

Study Medication will be supplied to patients as powder in a foil pouch. Patients will open the pouch by hand using a fold-over tear notch or by using scissors to cut across the top of the pouch. The dose solution should be prepared daily by dissolving the entire contents of a single pouch in approximately a half-glass or half-cup of water and mixing with a spoon for approximately 30 seconds until dissolved. Upon completion of preparation, the dose solution is colorless and slightly hazy in appearance. The dose solution should be consumed immediately.

Patients will take the first dose of Study Medication in the clinic on Day 1 and will be instructed to continue taking Study Medication once daily with food, for a total of 12 weeks. Patients should be instructed to take Study Medication at approximately the same time each day. If a dose is missed, the patient should resume dosing as soon as possible. The patient should not take

two doses at the same time. Deviations from prescribed dosing should be discussed at each visit for assessment of compliance and retraining when necessary.

10.3.4. Study Medication Return and Disposal

The Sponsor or designee will review with the Investigator and relevant site personnel the process for Study Medication return, disposal, and/or destruction, including responsibilities for the site versus the Sponsor (or designee). Specific requirements for destruction or return can be found in the Pharmacy Manual.

10.3.5. Study Medication Accountability

To satisfy regulatory requirements regarding drug accountability, all Study Medication will be reconciled in full. The Investigator or designee must maintain accurate records of the receipt of Study Medication, including date received, lot number, amount received, condition of the package, and the disposition of Study Medication.

Current dispensing records will also be maintained, including the date and amount of medication dispensed to each individual patient. Returned Study Medication records will be maintained and final Study Medication reconciliation will also be recorded for each patient.

10.4. Concomitant Medications and Procedures

All patients will be instructed to take their standard AP medication throughout the study. All medications, including the standard AP medication and over-the-counter therapies (e.g., vitamins, herbal, and nutritional supplements), taken at the time of the Screening Visit (Week -5 Visit) through the Follow-Up Visit will be recorded in the patient's source documentation and documented in the eCRF.

Any concomitant medication deemed necessary for the wellbeing of the patient may be given at the discretion of the Investigator. Use of medications that are prohibited per protocol may lead to patient withdrawal from the study.

A list of allowed and prohibited concomitant medications is shown in APPENDIX A.

11. STUDY ASSESSMENTS

The Schedule of Assessments is presented in Table 6 and should be referenced for details regarding the collection of each assessment at each visit in the respective study periods. Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, clinical laboratory blood draws may be performed by a Home Health Care service provider or by a local laboratory; other safety and efficacy assessments may be performed remotely via phone/audio or video conferencing platforms (with the exception of Facebook).

Study personnel should strive to perform assessments within the visit window as shown in Table 6 with the understanding that not all assessments may be able to be performed. Safety-related assessments must be prioritized. Missed assessments will be recorded in the eCRF with notation that the missed assessment was due to the COVID-19 pandemic. In case of two consecutive missed safety assessments, continued patient participation in the study must be discussed by the Investigator and the Medical Monitor.

11.1. Demographic Characteristics and Medical History

Demographic characteristics (i.e., sex, ethnic origin, date of birth, and calculated body mass index) will be collected and detailed on the eCRF.

At Week -5, the patients must have a confirmed DSM-V diagnosis of schizophrenia for the past 2 years based on patient's history and also confirmed by psychiatric evaluation and MINI International Neuropsychiatric Interview Psychotic Disorders, version 7.0.2 (MINI, Version 7.0.2; see APPENDIX L).

11.2. Physical Examination

A full physical examination will include an examination of all major organ systems. Brief physical examinations will be symptom-directed.

11.3. Vital Signs

Vital signs will be measured after the patient has been in a supine or semi-supine position for at least 5 minutes and will include blood pressure, pulse rate, respiratory rate, and temperature.

Weight and height will be measured and used to calculate the patient's BMI Weight and height will be converted as needed to kilograms and centimeters, respectively, prior to statistical analyses.

11.4. Electrocardiogram (ECG)

Twelve-lead electrocardiograms will be performed after the patient has rested in a supine or semi-supine position for at least 5 minutes. Individual parameters including PR, QT, QTcF, QRS, and RR intervals will be collected. Repeat electrocardiograms (if deemed necessary) should be performed at least 5 minutes apart. The Investigator should indicate review of the electrocardiogram reports throughout the study by signing and dating each report.

11.5. Clinical Laboratory Assessments

Clinical laboratory assessments will include serology, hematology, coagulation laboratory parameters, serum chemistry, serum renal laboratory parameters, complete urinalysis, urine pregnancy test, urine drug screen and alcohol breath test. The list of specific tests is shown in APPENDIX B. Samples for laboratory assessments should be collected at the beginning of the Study Visit and prior to the dose.

The results of the laboratory tests conducted at Week -5 must be assessed by the Investigator to determine each patient's eligibility for participation in the study. The Investigator should indicate review of the laboratory reports throughout the study by signing and dating each report.

Where applicable, laboratory results that fall outside the reference range will be interpreted by the Investigator as Abnormal, not clinically significant, or Abnormal, clinically significant. Laboratory results deemed Abnormal, clinically significant will be recorded as an adverse event in the eCRF and should be fully investigated and repeated for verification. Clinically significant laboratory abnormalities requiring intervention should be discussed with the Medical Monitor. Additional tests and evaluations required to establish the significance or etiology of a clinically significant abnormal result or to monitor the course of an adverse event should be obtained when clinically indicated. Whenever possible, the etiology of the clinically significant abnormal findings will be documented on the eCRF.

Any significant laboratory abnormalities that are either serious or unexpected will be promptly reported to the Sponsor. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be reported to the Sponsor or designee.

11.6. Assessment of Efficacy

11.6.1. Positive and Negative Symptom Scale (PANSS)

The PANSS is a psychiatric rating scale designed to measure symptom severity among patients with schizophrenia over the preceding 7 days. The PANSS items are divided into positive, negative and general psychopathology factors utilizing a 30-item, 7-point rating scheme. Scoring instructions will be provided (to the Rater) with each item accompanied by a complete definition as well as detailed anchoring criteria for all 7 rating points, which represent increasing levels of psychopathology: 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe and 7= extreme. The PANSS is scored by summation of ratings across items such that the potential ranges are 7 to 49 for each of the Positive and Negative Scales and 16 to 112 for the General Psychopathology Scale. The PANSS total score is the score of all 30 PANSS items taken together. (see APPENDIX C)

11.6.2. Clinical Global Impression-Severity (CGI-S) Score

The CGI-S rating scale is a commonly used measure of symptom severity and treatment response. The severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment. (see APPENDIX D)

11.6.3. Personal and Social Performance Scale (PSP)

The PSP is measure of personal and social functioning of patients with psychiatric disorders. The scale is a hundred-item scale, divided in 10 similar intervals. The score is based on the assessment of a patient's performance in four categories: socially useful activities, personal and social relationships, self-care, disturbing and aggressive behavior. (see APPENDIX E)

11.6.4. Schizophrenia Quality of Life Scale (SQLS)

The SQLS is a self-report Quality of Life scale developed specifically for patients with schizophrenia. It is a 30-item questionnaire comprised of three domains ('psychosocial', 'motivation and energy', and 'symptoms and side-effects'). (see APPENDIX F)

11.7. Extrapyramidal Symptoms

11.7.1. Simpson-Angus Scale (SAS)

The SAS consists of a list of 10 symptoms of parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item is rated on a 5-point scale, with a score of one representing absence of symptoms, and a score of 5 representing a severe condition. The SAS total score is the sum of the scores for all 10 items. (see APPENDIX G)

11.7.2. Abnormal Involuntary Movement Scale (AIMS)

The Abnormal Involuntary Movement Scale (AIMS) is a 10-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients taking neuroleptic medications. Body areas of interest include Facial and Oral, Extremities and Lower, and Trunk. Each item is scored on an ordinal scale that ranges from 0 to 4: none, minimal, mild, moderate, or severe. Additional global items assess the overall severity, tardive dyskinesia-associated functional impairment, and the patient's level of awareness of the movements and distress associated with them. (see APPENDIX H)

11.7.3. Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Rating Scale (BARS) consists of 4 items related to akathisia: objective observation of akathisia by the Investigator, subjective feelings of restlessness by the patient, distress due to akathisia, and global evaluation of akathisia. The first 3 items are rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation is made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, patients are observed while they were seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (e.g., while engaged in neutral conversation or engaged in activity on the ward) are also rated. Subjective phenomena are to be elicited by direct questioning. (see APPENDIX I)

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

The Columbia Suicide Severity Rating Scale (C-SSRS) is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. There are 2 versions of the scale being used in this protocol. (see APPENDIX J)

11.9. Antipsychotic (AP) Medication Blood Level

Blood samples will be taken to assess blood levels of the AP medication being taken by the patient. The confirmation of levels of one of the AP medications listed in APPENDIX A will be required to be eligible for randomization to the Treatment Period. The details on collection, processing, storage and shipping of blood samples for AP assessment can be found in the study Laboratory Manual.

11.10. CTP-692 Blood Level

CTP-692 blood levels will be measured following study completion. The details on collection, processing, storage and shipping of blood samples for CTP-692 assessment can be found in the study Laboratory Manual.

11.11. Genetic Testing

A blood sample for genetic testing is optional. Only one blood sample is required for genetic testing. The genetic markers analyzed may be related to clinical symptoms, and/or other factors as determined by the Sponsor. The details on collection, processing, storage and shipping of blood samples for genetic testing can be found in the study Laboratory Manual.

11.12. Unscheduled Visit

In addition to regularly scheduled protocol visits, an Unscheduled Visit may be conducted to ensure appropriate safety monitoring or follow-up of the patient, at the discretion of the Investigator. For example, an Unscheduled Visit may be scheduled to monitor potential or actual clinically meaningful safety laboratory results or for other clinical signs, symptoms, or considerations that warrant additional safety follow-up. An Unscheduled Visit may also be conducted to accommodate repeat testing of non-safety related laboratory assessments. Only those criteria requiring additional monitoring should be performed at the Unscheduled Visit. An Unscheduled Visit will not replace regularly scheduled protocol visits.

12. ADVERSE EVENTS

12.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an adverse event. A diagnosis or syndrome should be recorded on the adverse event page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. A worsening of the condition under study will not be reported as an adverse event.

All patients will be monitored for adverse events during the study. Assessments may include monitoring of the following parameters: the patient's clinical symptoms, laboratory, physical examination findings, or findings from other tests and/or procedures.

An adverse event reported after informed consent, but before the first dose of Study Medication (i.e., Day 1), will be considered a pretreatment adverse event and will be captured on the eCRF. Adverse events will be considered treatment-emergent if the onset is after the first dose of Study Medication.

An abnormal laboratory value is considered to be an adverse event if the abnormality:

- results in discontinuation from the study;
- is judged by the Investigator to be of significant clinical importance requiring treatment, modification/interruption of investigational product dose, or any other therapeutic intervention.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the adverse event eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the adverse event. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

12.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to seriousness, severity/intensity, and relationship to Study Medication, duration, action taken, and outcome.

12.2.1. Serious Adverse Event (SAE)

A serious adverse event is an adverse event, as per Title 21 CFR 312.32 and ICH E2A.II.B that fulfills the following criteria:

- Is fatal (results in death);
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; or
- Constitutes an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Events **not considered** to be serious adverse events are hospitalizations for:

- A procedure for protocol/disease-related investigations (e.g., sampling for laboratory tests). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- A procedure that is planned (i.e., planned prior to the starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable serious adverse event.
- An elective treatment of or an elective procedure for a pre-existing medical condition that does not worsen.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an adverse event is considered serious, the adverse event eCRF must be completed.

For each serious adverse event, the Investigator will provide information on severity, start and stop dates, relationship to investigational product, action taken regarding investigational product, and outcome.

Queries pertaining to serious adverse events will be handled through the electronic data capture system or other appropriate means. Urgent queries (e.g., missing causality assessment) may be handled by telephone.

12.2.2. Severity/Intensity

For both adverse events and serious adverse events, the Investigator must assess the severity/intensity of the event.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to grade the severity/intensity of all events. These criteria will be provided in a study manual. If a CTCAE criterion does not exist, the Investigator should grade the severity according to the following criteria:

- Grade 1 (mild): does not interfere with the patient's usual function
- Grade 2 (moderate): interferes to some extent with patient's usual function
- Grade 3 (severe): interferes significantly with patient's usual function
- Grade 4 (life-threatening): results in a threat to life or in an incapacitating disability
- Grade 5 (death): results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

12.3. Relationship to Study Medication

Relationship should be assessed and provided for every adverse event/serious adverse event based on currently available information. Relationship is to be reassessed and provided as additional information becomes available. Adverse events will be classified by the Investigator as follows:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event resolves or improves upon withdrawal of drug (de-challenge). The event would be considered as definitely related to the Study Medication upon results of a positive re-challenge procedure.

Probably Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors that may have contributed to the event (e.g., the patient's clinical condition, other

concurrent disease, concomitant medications or events) is unlikely, and the event follows a clinically reasonable response upon withdrawal of drug (de-challenge).

Possibly Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the Study Medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events).

Unlikely Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).

Not related: The adverse event is completely independent of Study Medication administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

12.3.1. Duration

For all adverse events whether or not considered serious, the Investigator will provide a record of the start and stop dates of the event. Every effort should be made to resolve all adverse events with continued follow-up with the patient until appropriate resolution can be achieved. If an event is unresolved at the end of the study it will be recorded as ongoing.

12.3.2. Action Taken

The Investigator will record the action taken with investigational product as a result of an adverse event or serious adverse event on the eCRF, as applicable (e.g., discontinuation, or interruption of investigational product, as appropriate) and record if concomitant and/or additional treatments were given for the event.

12.3.3. Outcome

The Investigator will record the outcome of adverse events on the eCRF, as applicable (e.g., recovered, recovered with sequelae, not recovered, or death (due to the adverse event).

12.3.4. Follow-Up

Adverse events assessed as not related to Study Medication, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events assessed as related to Study Medication and serious adverse events will be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, is otherwise explained, death occurs, or the patient is lost to follow up. If resolved, a resolution date should be provided. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the

adverse event. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

12.3.5. Pregnancy

The Sponsor must be informed within 24 hours upon learning that a patient, or male patient's partner, has become pregnant any time after the first dose of Study Medication until 4 weeks after the last dose of Study Medication. Patient pregnancies (or pregnancy of a male patient's partner) must be followed until termination of pregnancy or the birth of the child.

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking the investigational product should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

12.3.6. Recording Adverse Events

All adverse events (regardless of seriousness or relationship to Study Medication) including those from the time informed consent is obtained through to the final study visit are to be recorded in the eCRF. Each individual adverse event is to be listed as a separate entry. The Investigator will provide information about dates of onset and resolution, seriousness, severity, action(s) taken, outcome, and relationship to the Study Medication. All adverse events should be documented in the patient's source documents.

12.3.7. Reporting Adverse Events

The Investigator must report to Sponsor or its designee all adverse events that occur during the study from the time written informed consent is given until the final study visit or early termination, regardless of their relationship to the Study Medication. Serious adverse events and pregnancies will be reported from the time written informed consent is given through 4 weeks beyond the last dose of Study Medication.

12.3.8. Reporting Serious Adverse Events

The Investigator is required to notify the Sponsor, and the Sponsor's designated Drug Safety Unit within 24 hours after becoming aware of the occurrence of a serious adverse event. All serious adverse events will be reported through completion of the adverse event eCRF. The Investigator will be responsible for reporting serious adverse events to the IRB.

[redacted] **Emergency Contact Information:**

Dr. [redacted]

Phone: [redacted]
e-mail: [redacted]

[redacted]
e-mail [redacted]
Fax: [redacted]

If an Investigator becomes aware of a serious adverse event within 4 weeks after the last dose of Study Medication and it is considered by him/her to be caused by the Study Medication with a reasonable possibility, the event must be documented and reported through completion of the adverse event eCRF.

12.3.9. Reporting Urgent Safety Issues

If the study site staff becomes aware of an actual or potential urgent safety issue, then the Sponsor and Sponsor's designee (Medical Monitor) must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of patients participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include: (1) issues with an investigational drug or comparators; (2) study procedures; (3) inter-current illness (including pandemic infections); (4) concomitant medications; (5) concurrent medical conditions; or (6) any other issues related to the safe conduct of the study or that pose a risk to study patients.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, the Investigators may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

13. STATISTICAL METHODS

Additional details for statistical methods and analysis will be provided in the Statistical Analysis Plan.

13.1. Sample Size Rationale

Approximately 75 patients will be randomized to each treatment arm to achieve a sample size of approximately 60 patients per arm who complete the study. A sample size of 60 per arm provides at least 80% power for a treatment difference of 5.2 (standard deviation of 10) between Week 12 and Baseline in PANSS total score, on a two-sided t-test at 0.05 significance level.

13.2. Endpoints

13.2.1. Efficacy

The primary efficacy endpoint will be the change in PANSS total score at Week 12 from Baseline

Secondary efficacy endpoints include:

- Change in CGI-S score at Week 12 from Baseline
- Change in PSP score at Week 12 from Baseline

Exploratory efficacy endpoints include:

- Change in PANSS total score at Weeks 2, 4, 8, and 10 from Baseline
- Change in PANSS Positive Symptoms Factor Score (PSFS) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS Negative Symptoms Factor Score (NSFS) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in CGI-S score at Weeks 2, 4, 6, 8, and 10 from Baseline
- Change in PSP score at Week 6 from Baseline
- Change in Schizophrenia Quality of Life (SQLS) at Week 12 from Baseline

13.2.2 Safety

Safety of CTP-692 will be assessed by evaluating adverse events, vital signs, concomitant medications, clinical laboratory parameters including blood urea nitrogen (BUN) and creatinine, urinalysis, ECG results, as well as physical examinations. Extrapyramidal symptoms (EPSs) will be evaluated using SAS, AIMS, and the BARS. Assessment of suicidality will be performed at every visit using the C-SSRS.

13.3. Analysis Populations

The Safety Population will include all randomized patients who receive at least one dose of Study Medication. The Efficacy Population will include all patients who receive Study Medication and have at least one post-baseline PANSS assessment during the Treatment Period. The Per Protocol analysis population will include all patients in the Efficacy Population who were dosed according to protocol with no major protocol deviations.

13.4. Analyses

For the Treatment Period, data will be summarized by treatment group (CTP-692 1 g QD, CTP-692 2 g QD, CTP-692 4 g QD, or placebo). All data for analysis will be listed by patient.

Continuous measures will be summarized descriptively (mean, median, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

Additional details for statistical methods will be provided in the Statistical Analysis Plan.

13.4.1. Disposition and Baseline Characteristics

Disposition will be summarized by randomized treatment group. The number and percentage of patients, who are randomized, treated, prematurely discontinued (overall and by reason), and complete the study will be summarized.

Baseline characteristics will be summarized by treatment group.

The number of patients in each treatment group will be summarized for each investigative site for each analysis population. Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term. Medical history and concomitant medications will be summarized for the Safety Population.

13.4.2. Efficacy

All statistical tests will be 2-sided with a significance value of 0.05. Patients will be summarized by randomized treatment group. There will be no adjustments for multiple comparisons to placebo.

A mixed effects repeated measures model will be used to assess treatment group differences for change from baseline. The model will include treatment group, analysis visit, treatment-by-visit interaction, the baseline value as a covariate, and patient as a random effect. The comparison of each CTP-692 dose group versus placebo will be assessed by forming the least squares means estimate of each the CTP-692 dose group and comparing it to the placebo group at each postbaseline analysis visit. An unstructured covariance structure will be used to model the within-patient errors.

As a sensitivity analysis, the last observation carried forward (LOCF) method will be used to impute missing values for patients who withdraw from the study prior to the completion of the 12-week Treatment Period.

Additional details will be summarized in the Statistical Analysis Plan.

13.4.3. Study Medication Compliance

Study Medication compliance will be summarized for each treatment group. The number of days of Study Medication administration will be summarized for each treatment group.

Study Medication compliance will be measured by the percentage of scheduled doses that were taken. Descriptive statistics will be used to summarize the dosing compliance percentage within each treatment group.

13.4.4. Safety

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. Patients will be summarized according to the study medication received (i.e., as treated), should it differ from the randomized treatment arm. All safety endpoints will be listed in by-patient data listings.

Adverse events will be coded using MedDRA and summarized by system organ class and preferred term. Clinically significant deteriorations in physical examination findings will be reported and summarized as adverse events. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events.

13.4.5. Adverse Events

An adverse event reported after informed consent, but before the first dose of Study Medication (i.e., Day 1), will be considered a pre-treatment adverse event. Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that occurs after administration of the first dose of Study Medication or AEs noted prior to the first Study Medication administration that worsen after Baseline. The number and percentage of patients who report TEAEs will be summarized by system organ class and preferred term. Treatment emergent adverse events will also be summarized by intensity as well as relationship to Study Medication. For summaries by relationship, relationship will be dichotomized as related (possibly, probably, and definitely related) or not related.

Patients who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to Study Medication when summarized by relationship. If a patient reports multiple preferred terms for a system organ class, the patient will be counted only once for that system organ class.

Proportions for adverse events that are gender-specific (e.g., dysmenorrhea) will be based on the number of patients from that gender.

The number and percentage of patients who experience TEAEs will be summarized by treatment group for the following:

- By system organ class and preferred term
- By severity/intensity, system organ class, and preferred term
- By relationship to Study Medication (related, not related), system organ class, and preferred term
- Serious adverse events by system organ class and preferred term
- Serious adverse events by relationship to Study Medication, system organ class, and preferred term
- Adverse events resulting in discontinuation of Study Medication by system organ class and preferred term
- Adverse events that result in Study Medication dose interruption by system organ class and preferred term

By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment. Treatment-emergent adverse events that result in dose interruption will also be identified.

13.4.6. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized descriptively. Only the following specific suicidal ideation and behavior category questions with any "Yes" responses will be summarized in a frequency distribution table at each post-randomization visit:

- Any Suicidal Ideation Category:
  - Wish to be Dead
  - Non-Specific Active Suicidal Thoughts
  - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
  - Active Suicidal Ideation with Some Intent to Act, without Specific Plan
  - Active Suicidal Ideation with Specific Plan and Intent
- Any Suicidal Behavior Category:
  - Completed Suicide
  - Non-Fatal Suicide Attempt
  - Interrupted Attempt
  - Aborted Attempt
  - Preparatory Acts or Behavior

- Any Suicidal Ideation or Behavior Category

13.4.7. Clinical Laboratory

Patients with clinically significant abnormal laboratory values will be identified. Clinically significant, treatment-emergent laboratory values (i.e., baseline < Grade 3 and post-baseline meets ≥ Grade 3, according to CTCAE, version 5.0) will be summarized by treatment group. Laboratory values will be summarized at each time point for each treatment group, using descriptive statistics.

13.4.8. Vital Signs

Vital signs will be summarized at each time point for each treatment group, using descriptive statistics. Change from baseline in vital signs values will also be summarized.

Baseline will be defined as the last vital sign value obtained before the first dose of Study Medication on Day 1.

13.4.9. Electrocardiogram

The change from baseline in ECG intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group.

Frequency distributions of the QTcF interval will be displayed by treatment group for abnormally high values that are greater than their baseline value at any post-baseline visit and the following data cuts:

>450 msec and > Baseline value

>470 msec and > Baseline value

>500 msec and > Baseline value

Additionally, the change from baseline frequency distributions of the QTcF interval will displayed by treatment group for the following data cuts:

>30 msec increase

>60 msec increase

14. REGULATORY CONSIDERATIONS

It is the responsibility of the clinical site and staff to notify the Sponsor and Sponsor's designee immediately upon becoming aware of a serious breach of GCP or of the study protocol. It is the responsibility of the Sponsor or its designee to notify appropriate regulatory authorities of any serious breach which is likely to effect, to a significant degree, the safety or mental integrity of the patients of the study or the scientific value of the study.

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from the IRB prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Sponsor's Responsibilities

The Sponsor or its designee is responsible for the following:

- Selecting qualified Investigators
- Providing Investigators with the information they need to properly conduct an investigation
- Ensuring proper monitoring of the investigation
- Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding adverse events or risks associated with the medication being studied

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from Concert Pharmaceuticals or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts). Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, source data verification may be performed remotely.
- Record and report any protocol deviations.
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to the Sponsor and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

As the Sponsor, Concert Pharmaceuticals has delegated some responsibilities to a designee, or Contract Research Organization.

14.3. Investigator's Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Each Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the Study Medication, and their study-related duties and functions. The Principal Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible from conducting or working on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Concert Pharmaceuticals. The Investigator is required to immediately disclose to the Sponsor in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by the FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The Investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator should inform the IRB of any event likely to affect the safety of patients or the continued conduct of the study, in particular any change in safety. Additionally, all updates to

the IB will be sent to the IRB. A progress report will be sent to the IRB and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by the IRB or local regulations.

The Investigator will maintain a copy of all correspondence with the IRB, including copies of approved documents. The Investigator will also maintain a copy of the IRB membership list with occupation and qualification (or a statement confirming compliance with GCP requirements for committee composition).

The Investigator will notify the IRB of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to the IRB will also be sent to the Sponsor along with the completed electronic case report forms (eCRFs) and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

14.4. Protocol Amendments

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. All amendments to the protocol will be written by the Sponsor. The Investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB. Except for administrative amendments, Investigators must await IRB approval of protocol amendments before implementing the change(s). The Sponsor will ensure submission of any protocol amendments to the appropriate regulatory agencies.

In light of the FDA issued Guidance for Industry, Investigators, and Institutional Review Boards, entitled "Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" trial conduct may be impacted by the COVID-19 pandemic. Challenges may arise (e.g., quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, etc) leading to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-specified visits and laboratory/diagnostic testing. To minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) amendments to protocol defined criteria may be implemented prior to IRB approval or before filing an amendment to the IND.

Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the study. However, a protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, and the IRB notified within 5 days.

When, in the judgment of the chairman of the local IRB, the Investigators, and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written ICF will require similar modification. In such

cases, repeat informed consent will be obtained from patients enrolled in the study before continued participation under the new amendment.

14.5. Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s) or remotely. Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

14.6. Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

A quality control and quality assurance plan addressing aspects of the study that may impact data integrity or the protection of human subjects may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

In light of the COVID-19 pandemic, patient safety will be ensured by maintaining compliance with Good Clinical Practice (GCP) and minimizing risks to patient safety and data integrity. These efforts include additional risk mitigation strategies and appropriate documentation of protocol deviations occurring prior to implementation of protocol amendments.

15. DATA HANDLING AND RECORDKEEPING

15.1. Confidentiality

All information disclosed or provided by the Sponsor (or designee), or generated or produced during the study including, but not limited to, the protocol, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the study, are confidential. The Investigator or any person under his/her authority agrees to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

Submission of this protocol and any other necessary documentation to the IRB is expressly permitted, IRB members having the same obligation of confidentiality. Authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site. Study Medication, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and responsible ethics committee(s) or regulatory authorities.

Patients' names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the patient are to remain at the site. This information will not be transferred to the Sponsor nor be contained in regulatory filings.

15.2. Patient Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., protected health information authorization).

Patients will be identified only by unique patient numbers in eCRFs and other datasets generated for this study. The patient will not be identified by name in the eCRF, in any study samples or study reports. All data generated in this study is for research purposes only. The Sponsor, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

The Sponsor will protect individual patient information to the fullest extent possible during this study. At no time will a patient become identified in any publication or presentation. However, the patient may have to become identified in the event of a regulatory authority audit or inspection in order to verify the accuracy of the data. Access to patient information is at the discretion of the Sponsor and cannot occur prior to database lock or other specified events as determined solely by the discretion of the Sponsor.

15.3. Data Collection

All data obtained for analysis in the clinical study described in this protocol will use an electronic data capture system. Data reported in the eCRFs should be consistent with and substantiated by the patient's medical record and original source documents. Any discrepancies must be explained.

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

15.4. Case Report Form Completion

Data within the eCRF will be monitored by a Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the Sponsor's designee and the Sponsor may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The completed eCRF for each patient must be signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the eCRF and certifies it to be complete and accurate. In light of the COVID-19 pandemic, study eCRFs will be modified to incorporate changes to study procedures (e.g., missed assessments, remote visits, etc.).

15.5. Database Management, Data Clarification, and Quality Assurance

The Sponsor's designee (i.e., a designated Contract Research Organization) will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document, and provide it to the Sponsor for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Quality control procedures will be conducted prior to database lock according to the designated Contract Research Organization standard operating procedures.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between the Sponsor, Statistician, Data Manager, and Quality Assurance Auditor according to designated standard operating procedures of the Contract Research Organization.

15.6. Inspection of Records

According to the ICH guidelines for GCP, the Sponsor or designee must verify data entered in the eCRF entries against the source documents. The objective of source document verification is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that source documents are an accurate and confirmable reflection of the patient's evaluations during participation in the study and that all relevant information recorded in the source document is accurately entered into the eCRF. All source documents should be correctly labeled and filed and associated with a single, verifiable patient.

All data required for this study should be captured in source notes. No data obtained by the Investigator or other study personnel should be captured directly in the eCRF. All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not compliant with applicable regulatory guidance, they are not considered a valid source for this study. All patient progress notes must be dated and signed at the time of the visit. The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

- Information to confirm that the patient exists (e.g., initials, date of birth, and sex);
- Confirmation that the patient satisfies the inclusion/exclusion criteria;
- Confirmation that the patient is taking part in the clinical study;
- Confirmation of the informed consent process;
- Visit dates and documentation of protocol assessments and procedures;
- Information concerning all adverse events;
- Details of concomitant and investigational medications.

Source document verification is not a substitute for clinical study monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, source document verification has been carried out, and the study timelines and enrollment goals and requirements have been met. In light of the COVID-19 pandemic. source document verification may occur remotely. Additional detail on remote source document verification will be documented separately in the Trial Master File.

15.7. Retention of Records

For investigational drug studies, clinical Investigators must retain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed upon designee.

16. PUBLICATION POLICY

The results of this study may be published in a medical publication, journal, or another public dissemination, or may be presented at a medical conference or used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

17. LIST OF REFERENCES

1. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Witeford HA. *Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease study 2016.* Schizophrenia Bulletin (2018): epub.
2. Lane HY, Lin CH, Green MF, Hellemann G, Huang CC, Chen PW, Tun R, Chang YC, Thai GE. Add-on treatment of Benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. JAMA Psychiatry (2013), 70 (12): 1267-1275.
3. Bugarski-Kirola D, Iwata N, Sameljak S, Reid C, Blaettler T, Millar L, Marques TR, Garibaldi G, Kanpur S. Efficacy and safety of adjunctive bitopertin versus placebo in patients with suboptimally controlled symptoms of schizophrenia treated with antipsychotics: results from three phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicenter studies in the SearchLyte clinical trial programme. Lancet Psychiatry (2016), 3: 1115-1128.
4. Balu DT, Coyle JT. *The NMDA receptor "glycine modulators site" in schizophrenia:* D-*serine, glycine, and beyond.* Curr Opin Pharmacol (2015), 20: 109-115.
5. Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, Nakazato M, Kumakiri C, Okada S, Hasegawa H, Imai K, Iyo M. *Evidence in support of the N-Methyl-*D*-Aspartate receptor hypofunction hypothesis of schizophrenia.* Arch Gen Psychiatry (2003), 60: 572-576.
6. Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. *Reduced* D-*serine to total serine ratio in the cerebrospinal fluid of drug naïve schizophrenic patients.* Progress in Neuro-Psychopharmacology and Biological Psychiatry (2005), 29: 767-769.
7. Cho SE, Na KS, Cho SJ, Kant SG. *Low* D*-serine levels in schizophrenia: a systematic review and meta-analysis.* Neuroscience Letters (2016), 634: 42-51.
8. Bendikov I, Nadri C, Amar S, Panizzutti R, De Miranda J, Wolosker H, Agam G. *A CSF and postmortem brain study of* D*-serine metabolic parameters in schizophrenia.* Schizophrenia Research (2007), 90: 41-51.
9. Tsai G, Yang Pinchen, Chen LC, Lange N, Coyle JT. D*-serine added to antipsychotics for the treatment of schizophrenia.* Biol Psychiatry (1998): 44(11):1081-1089.
10. Heresco-Levy U, Javitt DC, Ebstein R, Vass A, Lichtenberg P, Bar G, Catinari S, Ermilov M. *D-serine efficacy as add-on pharmacotherapy to Risperidone and Olanzapine for treatment-refractory schizophrenia.* Biol Psychiatry (2005), 57(6): 577-585.
11. Lane HY, Chang YC, Liu YC, Chiu CC, Tsai GE. *Sarcosine or* D*-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study.* Arch Gen Psychiatry (2005), 6(11): 1196-1204.
12. Lane HY, Lin CH, Juana YJ, Liao CH, Chang YC, Thai G. *A randomized, double-blind, placebo-controlled, comparison study of sarcosine (N-methylglycine) and* D*-serine add-*

on treatment for schizophrenia. International Journal of Neuropsychopharmacology (2010), 13(4): 451-460.

13. Kantrowitz JT, Malhotra AK, Cornblatt B, et al. *High dose* D-*serine in the treatment of schizophrenia.* Schizophrenia Research (2010), 121(1-3): 125-130.
14. Ermilov E, Gelfin E, Levin R, Lichtenberg P, Hashimoto K, Javitt D, Heresco-Levy U. *A pilot double-blind comparison of* D-*serine and high-dose olanzapine in treatment-resistant patients with schizophrenia.* Schizophrenia Research (2013), 150: 604-605.
15. Kantrowitz JT, Epstein ML, Lee M, Lehrfeld N, Nolan K, Shope C, Petkova E, Silipo G, Javitt D. *Improvement in mismatch negativity generation during* D-*serine treatment in schizophrenia: correlation with symptoms.* Schizophrenia Research. (2018), 191: 70-79.
16. Ganote CE, Peterson DR, Carone FA. *The nature of* D-*serine-induced nephrotoxicity.* American Journal of Pathology (1974), 77: 269-282.
17. Mothet JP, Parent AT, Wolosker H, Brady RO, Linden D, Ferris CD, Rogawski MA, Snyder SH. D-*serine is an endogenous ligand for the glycine site of the N-mehtyl* D-*aspartate receptor.* Proc Natl Acad Sci. (2000), 97(9) 4926-4931.
18. Verrall L, Burnet PWJ, Betts JF, Harrison PJ. *The neurobiology of* D-*amino acid oxidase and its involvement in schizophrenia.* Molecular Psychiatry (2010), 15(2): 122-137.
19. CTP-692 Investigator's Brochure, Concert Pharmaceuticals Inc., 2019.
20. Kantrowitz JT, Woods SW, Petkova E, Cornblatt B, Corcoran CM, Chen H, Silipo G, Javitt DC. D-*serine for the treatment of negative symptoms in individuals at clinical high risk of schizophrenia: a pilot, double-blind, placebo-controlled, randomised parallel group mechanistic proof-of-concept trial.* Lancet Psychiatry (2015), 2(5): 403-412.
21. Calcia MA, Madeira C, Algeria FV, Silva TCS, Tannos FM, Vargas-Lopes C, Goldenstein N, Brazil AM, Ferreira ST, Panizzutti R. *Plasma levels of* D-*serine in Brazilian individuals with schizophrenia.* Schizophrenia Research (2012), 142(1): 83-87.
22. Yamamori H, Hashimoto R, Fujita Y, Numata S, Fujimoto M, Ohi K, Umeda-Yano S, Ito A, Ohmori T, Hashimoto K, Takeda M. *Changes in plasma* D-*serine,* L-*serine, and glycine levels in treatment-resistant schizophrenia before and after clozapine treatment.* Neuroscience Letters (2014), 582: 93-98.
23. Lezak MD, Howieson DB, Loring DW. *Digit Symbol-Coding.* Neuropsychological assessment. New York: Oxford University Press (2004): 368–370.
24. Morehead RP, Poe WD, Williams JO, Lazenby ME. The Influence of Age and Species on the Nephrotoxic Action of DL-Serine. *American Journal of Pathology* (1946), 22: 658-659.

25. Nair S, O'Brien SV, Hayden K, Pandya B, Lisboa PJG, Hardy KJ, Wilding JPH. *Effect of a Cooked Meat Meal on Serum Creatinine and Estimated Glomerular Filtration Rate in Diabetes-Related Kidney Disease. Diabetes Care* (2014), 37: 483-487.

26. Pimenta E, Jensen M, Jung D, Schaumann F, Boxnick S, Truebel H. Effect of Diet on Serum Creatinine in Healthy Subjects During a Phase I Study. *Journal of Clinical Medicine Research* (2016), 8(11): 836-839.

18. APPENDICES

APPENDIX A: CONCOMITANT MEDICATIONS

ALLOWED MEDICATIONS	PROHIBITED MEDICATIONS
Antipsychotics Aripiprazole Asenapine Brexipiprazole Cariprazine Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Contraceptives (oral and implants) Non-antipsychotic sleep medications	ADD prescription medications ADHD prescription medications Clozapine Lithium

APPENDIX B: CLINICAL LABORATORY ASSESSMENTS

HEMATOLOGY (blood)	**SERUM CHEMISTRY (blood)**	**SERUM RENAL LABS (blood) and URINALYSIS (urine)**
Complete blood count (CBC) Platelet count White blood cell (WBC) count with differential	Alanine aminotransaminase (ALT; SGPT) Albumin (ALB) Alkaline phosphatase (ALK-P) Amylase Aspartate aminotransaminase (AST; SGOT) Total bilirubin Direct bilirubin Indirect bilirubin Calcium (Ca) Carbon Dioxide (CO_2) Chloride (Cl) Total cholesterol Creatine kinase (CK) Follicle-Stimulating Hormone (FSH) Gamma-glutamyl transferase (GGT) Glucose Lactic dehydrogenase (LDH) Lipase Magnesium Total protein Phosphorus Potassium (K) Sodium (Na) Uric acid	Serum Blood urea nitrogen (BUN) Serum creatinine eGFR Urine Bilirubin Glucose Ketones Nitrates Occult blood Protein Specific gravity Urobilinogen pH Leukocytes Microscopy Creatinine UACR Urine Volume
COAGULATION (blood)	**SEROLOGY SCREEN (blood)**	**URINE DRUG SCREEN**
Prothrombin time test (PT) Partial prothrombin time test (aPTT) International normalized ratio (INR)	Human immunodeficiency virus antibody (HIV-Ab) Hepatitis B surface antigen (HBsAg) Hepatitis C virus antibody (HCV-Ab)	Amphetamines/methamphetamines Barbiturates Benzodiazepines* Cocaine metabolites Methadone Phencyclidine Opiates
BREATH TEST	**PREGNANCY (urine)**	
Ethyl alcohol	hCG	

* Positive test at Week -5 and Week -3 allowed if drug is prescribed by a physician

APPENDIX C: POSITIVE AND NEGATIVE SYMPTON SCALE (PANSS)

PANS S RATIN G FORM

		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lackofjudgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

APPENDIX D: CLINICAL GLOBAL IMPRESSION (CGI-S) SCORE

Clinical Global Impressions-Severity (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not ill at all

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare.

APPENDIX E: PERSONAL AND SOCIAL PERFORMANCE SCALE (PSP)

PSP – WORKSHEET

Please rate the patient on his/her level of dysfunctioning during the **past 7 days**.
There are 4 main domains of dysfunctioning considered in this scale:

		Absent	Mild	Manifest	Marked	Severe	Very severe
a)	socially useful activities; including work and study	☐	☐	☐	☐	☐	☐
b)	personal and social relationships	☐	☐	☐	☐	☐	☐
c)	self-care	☐	☐	☐	☐	☐	☐
d)	disturbing and aggressive behaviours	☐	☐	☐	☐	☐	☐

There are two different sets of **operational criteria** to judge the degree of difficulties:
One for the **a-c** areas and one specific to the **d** area.

Degrees of severity areas a-c

(i) Absent

(ii) Mild: known only to someone who is very familiar with the person

(iii) Manifest: difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels

(iv) Marked: difficulties interfering heavily with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able to reach the previous level of functioning

(v) Severe: difficulties that make the person unable to perform any role in that area, if not professionally helped, or lead the person to a destructive role, however, there are no survival risks

(vi) Very severe: impairments and difficulties of such intensity to endanger the person's survival

Degrees of severity area d

(i) Absent

(ii) Mild: corresponding to mild rudeness, unsociability or whingeing

(iii) Manifest: such as speaking too loudly or speaking to others in a too-familiar manner or eating in a socially unacceptable manner

(iv) Marked: insulting others in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (e.g. stripping or urinating in public)

(v) Severe: frequent verbal threats or frequent physical assaults, without intention or possibility to severe injuries

(vi) Very severe: defined as frequent aggressive acts, aimed at or likely to cause severe injuries

Guidelines for PSP total score

71-100:	These ratings reflect only mild difficulties
31-70:	These ratings reflect varying degrees of disability
1-30:	These ratings reflect functioning so poor that the patient requires intensive support or supervision

PSP - SCORING GUIDELINES

Refer to the PSP Quick Reference Card for more details on scoring guidelines.

100-91	Excellent functioning in all four main areas. He/she is held in high consideration for his/her good qualities, copes adequately with life problems, is involved in a wide range of interests and activities
90-81	Good functioning in all four main areas, presence of only common problems or difficulties
80-71	Mild difficulties in one or more of areas **a-c**
70-61	Manifest, but not marked difficulties in one or more areas **a-c** or mild difficulties in **d**
60-51	Marked difficulties in one of areas **a-c**, or manifest difficulties in **d**
50-41	Marked difficulties in two or more, or severe difficulties in one of areas **a-c**, with or without manifest difficulties in **d**
40-31	Severe difficulties in one and marked difficulties in at least one of areas **a-c**, or marked difficulties in **d**
30-21	Severe difficulties in two of areas **a-c**, or severe difficulties in **d**, with or without impairment in areas **a-c**
20-11	Severe difficulties in all areas **a-d** or very severe in **d** with or without impairment in general areas **a-c**. If the person reacts to external prompts, the suggested scores are 20-16; if not, the suggested scores are 15-11.
10-1	Lack of autonomy in basic functioning with extreme behaviours but without survival risk (ratings 6-10) or with survival risk, e.g. death risk due to malnutrition, dehydration, infections, inability to recognize situations of manifest danger (ratings 5-1).

Score ☐☐☐

Repeat final score in the patient's CRF.

APPENDIX F: SCHIZOPHRENIA QUALITY OF LIFE SCALE (SQLS)

SQLS Items

1. I lack the energy to do things
2. I am bothered by my shaking/trembling.
3. I feel unsteady walking.
4. I feel angry.
5. I am troubled by a dry mouth.
6. I can't be bothered to do things.
7. I worry about my future.
8. I feel lonely.
9. I feel hopeless.
10. My muscles get stiff.
11. I feel very jumpy and edgy
12. I am able to carry out my day-to-day activities.
13. I take part in enjoyable activities.
14. I take things people say the wrong way.
15. I like to plan ahead.
16. I find it hard to concentrate.
17. I tend to stay at home.
18. I find it difficult to mix with people.
19. I feel down and depressed.
20. I find that I can cope.
21. My vision is blurred.
22. I feel very mixed-up and unsure of myself.
23. My sleep is disturbed.
24. My feelings go up and down.
25. I get muscle twitches.
26. I am concerned that I won't get better.
27. I worry about things.
28. I feel that people tend to avoid me.
29. I get upset thinking about the past.
30. I get dizzy spells.

APPENDIX G: SIMPSON-ANGUS SCALE (SAS)

Patient Name:_____ Date: _____

SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE

The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1. **Gait**: The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:
   - 0 Normal
   - 1 Diminution in swing while the patient is walking
   - 2 Marked diminution in swing with obvious rigidity in the arm
   - 3 Stiff gait with arms held rigidly before the abdomen
   - 4 Stooped shuffling gait with propulsion and retropulsion

2. **Arm Dropping:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:
   - 0 Normal, free fall with loud slap and rebound
   - 1 Fall slowed slightly with less audible contact and little rebound
   - 2 Fall slowed, no rebound
   - 3 Marked slowing, no slap at all
   - 4 Arms fall as though against resistance; as though through glue

3. **Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
   - 0 Normal
   - 1 Slight stiffness and resistance
   - 2 Moderate stiffness and resistance
   - 3 Marked rigidity with difficulty in passive movement
   - 4 Extreme stiffness and rigidity with almost a frozen shoulder

4. **Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)
   - 0 Normal
   - 1 Slight stiffness and resistance
   - 2 Moderate stiffness and resistance
   - 3 Marked rigidity with difficulty in passive movement
   - 4 Extreme stiffness and rigidity with almost a frozen elbow

5. **Wrist Rigidity or Fixation of Position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:
   - 0 Normal
   - 1 Slight stiffness and resistance
   - 2 Moderate stiffness and resistance
   - 3 Marked rigidity with difficulty in passive movement
   - 4 Extreme stiffness and rigidity with almost frozen wrist

6. **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:
   - 0 The legs swing freely
   - 1 Slight diminution in the swing of the legs
   - 2 Moderate resistance to swing
   - 3 Marked resistance and damping of swing
   - 4 Complete absence of swing

7. **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:
   - 0 The head falls completely with a good thump as it hits the table
   - 1 Slight slowing in fall, mainly noted by lack of slap as head meets the table
   - 2 Moderate slowing in the fall quite noticeable to the eye
   - 3 Head falls stiffly and slowly
   - 4 Head does not reach the examining table

8. **Glabella Tap**: Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
   - 0 0-5 blinks
   - 1 6-10 blinks
   - 2 11-15 blinks
   - 3 16-20 blinks
   - 4 21 and more blinks

9. **Tremor:** Patient is observed walking into examining room and is then reexamined for this item:
   - 0 Normal
   - 1 Mild finger tremor, obvious to sight and touch
   - 2 Tremor of hand or arm occurring spasmodically
   - 3 Persistent tremor of one or more limbs
   - 4 Whole body tremor

10. **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
    - 0 Normal
    - 1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
    - 2 When excess salivation is present and might occasionally result in difficulty speaking
    - 3 Speaking with difficulty because of excess salivation
    - 4 Frank drooling

APPENDIX H: ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

NAME: _____
DATE: _____
Prescribing Practitioner: _____

CODE: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 - Severe

INSTRUCTIONS:
Complete Examination Procedure (attachment d.) before making ratings

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date	RATER Date	RATER Date	RATER Date
Facial and Oral Movements	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows periorbital area, cheeks, including frowning blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	O 1 2 3 4
Extremity Movements	**5. Upper (arms, wrists,, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	**7. Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patient's report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	**11. Current problems with teeth and/or dentures**	No Yes	No Yes	No Yes	No Yes
	12. Are dentures usually worn?	No Yes	No Yes	No Yes	No Yes
	13. Edentia?	No Yes	No Yes	No Yes	No Yes
	14. Do movements disappear in sleep?	No Yes	No Yes	No Yes	No Yes

Final: 9/2000

APPENDIX I: BARNES AKATHISIA RATING SCALE (BARS)

Patient name: **Date of assessment:**

Patient ID: **Assessor:**

BARNES AKATHISIA RATING SCALE

Barnes TR (1989) A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 154: 672–676

1. Objective SCORE: _____

0. Normal, occasional fidgety movements of limbs.
1. Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet or swinging of one leg while sitting, *and/or* rocking from foot to foot or 'walking on the spot' when standing, *but* movements present for less than half the time observed.
2. Observed phenomena, as described in (1) above, which are present for at least half the observation period.
3. Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed.

2. Subjective: Awareness of restlessness SCORE: _____

0. Absence of inner restlessness.
1. Non-specific sense of inner restlessness.
2. Patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still.
3. Awareness of an intense compulsion to move most of the time *and/or* reports a strong desire to walk or pace most of the time.

3. Subjective: Distress related to restlessness SCORE: _____

0. No distress.
1. Mild.
2. Moderate.
3. Severe.

4. Global clinical assessment of akathisia SCORE: _____

0. Absent.
   No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia.
1. Questionable.
   Non-specific inner tension and fidgety movements.
2. Mild akathisia.
   Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
3. Moderate akathisia.
   Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing.
4. Marked akathisia.
   Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
5. Severe akathisia.
   The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

(end)

APPENDIX J: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) BASELINE/SCREENING VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e g , *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period This is different than a specific plan with time, place or method details worked out (e g thought of method to kill self but not a specific plan) Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself Intent does not have to be 100% If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt ***There does not have to be any injury or harm***, just the potential for injury or harm If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e g , gunshot to head, jumping from window of a high floor/story) Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting Once they ingest any pills, this becomes an attempt rather than an interrupted attempt Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger Once they pull the trigger, even if the gun fails to fire, it is an attempt Jumping: Person is poised to jump, is grabbed and taken down from ledge Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt This can include anything beyond a verbalization or thought, such as assembling a specific method (e g , buying pills, purchasing a gun) or preparing for one's death by suicide (e g , giving things away, writing a suicide note) ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0 No physical damage or very minor physical damage (e g , surface scratches) 1 Minor physical damage (e g , lethargic speech; first-degree burns; mild bleeding; sprains) 2 Moderate physical damage; medical attention needed (e g , conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel) 3 Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e g , comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures) 4 Severe physical damage; *medical* hospitalization with intensive care required (e g , comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area) 5 Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over) 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX K: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) SINCE LAST VISIT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e g , *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period This is different than a specific plan with time, place or method details worked out (e g , thought of method to kill self but not a specific plan) Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself Intent does not have to be 100% If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt ***There does not have to be any injury or harm***, just the potential for injury or harm If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e g , gunshot to head, jumping from window of a high floor/story) Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting Once they ingest any pills, this becomes an attempt rather than an interrupted attempt Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger Once they pull the trigger, even if the gun fails to fire, it is an attempt Jumping: Person is poised to jump, is grabbed and taken down from ledge Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt This can include anything beyond a verbalization or thought, such as assembling a specific method (e g , buying pills, purchasing a gun) or preparing for one's death by suicide (e g , giving things away, writing a suicide note) ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0 No physical damage or very minor physical damage (e g , surface scratches) 1 Minor physical damage (e g , lethargic speech; first-degree burns; mild bleeding; sprains) 2 Moderate physical damage; medical attention needed (e g , conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel) 3 Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e g , comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures) 4 Severe physical damage; *medical* hospitalization with intensive care required (e g , comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area) 5 Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over) 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX L: MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

Now I am going to ask you about unusual experiences that some people have.

K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES
	b	IF YES: do you currently believe these things?	NO	YES
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? CLINICIAN: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS **K1** TO **K4**. FOR EXAMPLE, RELIGIOUS, DEATH, DISEASE OR SOMATIC DELUSIONS, DELUSIONS OF GRANDIOSITY, JEALOUSY OR GUILT, OR OF FAILURE, INADEQUACY, RUIN, OR DESTITUTION, OR NIHILISTIC DELUSIONS.	NO	YES
	b	IF YES: do they currently consider your beliefs strange or unusual?	NO	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES
	b	IF YES TO **K6a**: have you heard sounds / voices in the past month?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES

K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES
	b	IF YES: have you seen these things in the past month?	NO	YES

CLINICIAN'S JUDGMENT

K8	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED, INCOHERENT OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K8	b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K9	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K9	b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K10	a	DID THE PATIENT EVER IN THE PAST HAVE NEGATIVE SYMPTOMS, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION)?	NO	YES
K10	b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW?	NO	YES
K11	a	ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K7a**, CODED YES? **AND IS EITHER:** MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST) **OR** MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES? **AND** HOW LONG HAS THE MOOD EPISODE LASTED? _____ HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? _____ IF SUCH A MOOD EPISODE IS PRESENT, CODE YES TO **K11a** ONLY IF THE MOOD DISTURBANCE IS PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE NO. IF NO TO **K11a** AND THE TOTAL DURATION OF THE MOOD EPISODE IS **LESS THAN** THE TOTAL DURATION OF THE PSYCHOTIC EPISODE, THEN CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO **K13**.	NO ↳ K13	YES

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM **K1a** TO **K7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST **2 WEEKS** OF HAVING THESE BELIEFS OR EXPERIENCE (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE **NO** TO THIS DISORDER.

IF THE ANSWER IS **NO** TO THIS DISORDER GROUPING, ALSO CIRCLE **NO** TO **K12** AND MOVE TO **K13**

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

LIFETIME

K12 a ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K7b** CODED YES?

AND IS EITHER:

MAJOR DEPRESSIVE EPISODE (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE (CURRENT) CODED YES?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE **NO** TO **K13** AND **K14** AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

CURRENT

K13 ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K8b**, CODED YES?

AND

ARE **2** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K10b**, CODED YES?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

K14 IS **K13** CODED YES?

OR

(ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K8a**, CODED YES?

AND

ARE **2** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K10a**, CODED YES

AND

DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?)

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED YES?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

Concert Pharmaceuticals, Inc.

CP692.2001

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CTP-692 as an Adjunctive Treatment in Adult Patients with Schizophrenia

Protocol Amendment # 1, 16 October 2019

Summary of Changes

This amendment includes the following changes to the CP692.2001 protocol:

Section(s)	Change	Reason
Synopsis and Section 9.2, Exclusion Criteria # 16	Changed wording from "Positive alcohol breath test at the Screening/Qualification Visit (Weeks -5, -3)" to "Positive alcohol breath test." Changed Note below Exclusion Criteria # 16 from "*A repeat alcohol breath test will be allowed within 48 hours of the first test*" to "*A repeat alcohol breath test will be allowed within 48 hours of the first test only at the first Screening Visit (Week -5).*"	To clarify that subjects with positive alcohol test during Screening Period and Day 1 will be excluded. To clarify that a repeat test is allowed only at the first Screening Visit at Week -5.
Synopsis, Criteria for Evaluation and Section 6, Study Objectives	Changed "Measures" to "Endpoints" and added additional details to Exploratory Endpoints.	To clarify all endpoints being assessed in the study and to keep consistent with Section 13.2.
Table 6, Schedule of Assessments	Added FSH assessment along with Serology and footnote "FSH test for post-menopausal women only." Added footnote "Patients must sign the optional genetic blood sample genetic research consent form."	To clarify FSH assessment at first Screening Visit only and requirements prior to assessments being conducted.
Section 8.2.2, procedures performed **Week 2 through Week 12**	Alcohol breath test: "*Patient will be discontinued if they test positive at any two visits during the treatment period*" changed to "*Patient may be discontinued if they test positive at any two visits during the treatment period*"	To allow for Investigator/Medical Monitor/Sponsor discussion and discretion prior to discontinuing patient

Section(s)	Change	Reason
Section 12.3.8, Reporting Serious Adverse Events	Added additional Emergency Contact Information	To provide more options for Reporting of Serious Adverse Events
Section 13.4.2, Efficacy analyses	Deleted "The percentage of responders will be estimated at Week 12 based on percent change in the PANNS total score from Baseline to Week 12. Four definitions of a responder will be summarized: ≥20%, ≥30%, ≥40%, and ≥50% decrease from Baseline. The difference between each CTP-692 group and the placebo group will be assessed with the chi-square test."	Responder analysis not planned and this section was inadvertently inserted in the protocol.
Section 13.4.3, Study Medication Compliance	Changed Section title from "Study Medication Exposure and Compliance" to Study Medication Compliance"	To clarify that this section refers to analysis of days of Study Medication administration and not blood levels of Study Medication
Section 17, List of References	Added reference for CTP-692 Investigator's Brochure.	CTP-692 Investigator's Brochure has been referred to in the main text of the protocol.
Appendix E	Replaced PSP Worksheet	To provide version with scoring guidelines

Additional administrative edits were also made for clarity.

Concert Pharmaceuticals, Inc.

CP692.2001

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CTP-692 as an Adjunctive Treatment in Adult Patients with Schizophrenia

Protocol Amendment # 2, 11 February 2020

Summary of Changes

This amendment includes the following changes to the CP692.2001 protocol:

Section(s)	Change	Reason
Synopsis, Study Design Methodology, and Section 7.1, Overall Study Design	Study participation extended from 18 weeks to up to 20 weeks. Added extension of Qualification Period for up to 2 weeks. Added footnote to Study Design schematic.	To allow for repeat laboratory testing for confirmation of eligibility.
Synopsis and Section 9.1, Inclusion Criteria # 9	Post-menopausal female defined as those who have had amenorrhea for at least 1-year (for inclusion in the study) and Follicle-Stimulating Hormone (FSH) level greater than 40 mIU/mL. Removed "estradiol level less than 30 pg/mL".	Previous versions of the protocol defined post-menopausal females as those who had amenorrhea for at least 2 years (for inclusion in the study) which is inconsistent with the ICF which states: "postmenopausal is defined as the permanent cessation of menstruation for at least 12 months" Estradiol level requirement removed as estradiol level is not being measured at Screening.
Section 8, Table 6, Schedule of Assessments	Removed "X" for AP blood sample collection at Weeks 2, 6 and 12	Data not required for study end-point analysis
Section 8.2.1, Screening Period Procedures at Week -3	Added extension of Qualification Period for up to 2 weeks.	To allow for repeat laboratory testing for confirmation of eligibility.

Section 8.2.2, procedures performed **Week 2 through Week 12**	Removed AP blood sample collection at Weeks 2, 6 and 12	Data not required for study end-point analysis
Section 9.3, Patient Withdrawal Criteria	Added patient withdrawal criteria if they: • Exhibit suicidal behavior as determined by an affirmative answer on items 4 or 5 on the C-SSRS	Requested by FDA
Section 11.1, Unscheduled Visit	Added: An Unscheduled Visit may also be conducted to accommodate repeat testing of non-safety related laboratory assessments.	To allow for repeat testing of non-safety related laboratory parameters.

Additional administrative edits were also made for clarity.