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STATISTICAL ANALYSIS PLAN

PROTOCOL: 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

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PRODUCT : CTP-692

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AMEMDMENT HISTORY

Not applicable

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ALB	Albumin
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Antipsychotic
aPTT	Partial Prothrombin Time Test
AST	Aspartate Aminotransferase
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
CO_2	Carbon Dioxide
COVID	Coronavirus disease
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DSM	Diagnostic and Statistical Manual
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EPS	Extrapyramidal symptoms
ET	Early Termination

Abbreviation or special term	Explanation
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
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
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
NSFS	Negative Symptoms Factor Score
PANSS	Positive and Negative Syndrome Scale
PR	Pulse Rate

Abbreviation or special term	Explanation
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
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SQLS	Schizophrenia Quality of Life
TEAE	Treatment-Emergent Adverse Event
UACR	Urine Microalbumin/Creatinine Ratio
ULN	Upper Limit of Normal
US	United States
ug	Microgram
WBC	White Blood Cell

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the Phase 2 study entitled “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 #3: 14 April 2020). Mock shells will be produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the clinical study report (CSR).

2 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:

2.1 Primary Efficacy Endpoint

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

2.2 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

2.3 Exploratory Endpoints

- Change in PANSS total score at Weeks 2, 4, 8 and 10 from Baseline
- Change in PANSS Positive Symptoms Factor Score (PSFS; items P1-P7) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS Negative Symptoms Factor Score (NSFS; items N1-N7) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in General Psychopathology Symptoms Factor Score (items G1-G16) at Weeks 2, 4, 8, 10 and 12 from baseline
- Change in PANSS Cognitive Symptoms (items P2, N5, G5, G10, G11) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in Marder Negative Symptoms Factor Score (Marder NSFS; items N1, N2, N3, N4, N6, G7, G16) at Weeks 2, 4, 8, 10, and 12 from Baseline

- Change in PANSS total score at Week 12 from the average of the Screening, Qualification, and Day 1 pre-dose assessments
- 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

2.4 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)

3 STUDY DESIGN

3.1 Duration of Study

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), a 12-week Treatment Period and a Safety Follow-Up Visit approximately 1 week after the last dose of Study Medication.

3.2 Number of Participants (Study Population)

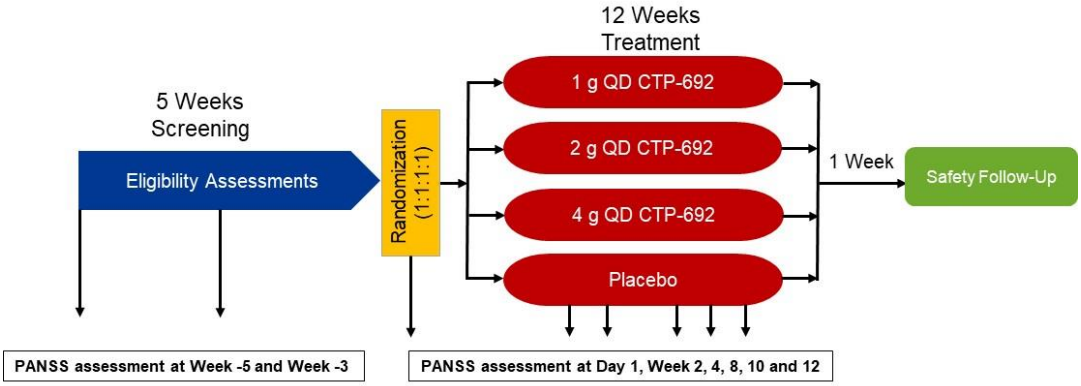
An estimated 300 patients will be enrolled at approximately 22 study sites in the United States.

3.3 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 (MINI International Neuropsychiatric Interview). Adult 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, Day -35), 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 (Week -3). Patients who continue to meet eligibility criteria based on assessments at the

Screening and Qualification visits and Day 1 (Baseline) 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 1. 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, vital signs, adverse-events and concomitant medications as shown in Table 1. 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 deems necessary. Patients who experience intolerable symptoms during the Treatment Period may discontinue the study at the discretion of the Investigator.

3.3.1 *Schedule of Assessments*

The schedule of study assessments is presented in Table 1.

Table 1. 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	

	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]													
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	
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

	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]													

[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.

3.4 Treatment

Evaluation of three (3) doses of 1 g, 2 g, and 4 g CTP-692 are planned, in addition to placebo.

3.5 Randomization and Blinding

The allocation to treatment sequence will be based on a randomization schedule generated by an independent statistician. The randomization schedule will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding.

The active and placebo treatments are identical in appearance within each group and matched placebo will be administered as necessary to maintain the blind.

3.6 COVID-19 Considerations

Due to the COVID-19 pandemic, some assessments may be conducted remotely. These will be treated the same as on-site assessments and will be aggregated with data from the on-site assessments for analysis.

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.

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. 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.

3.6.1 *Screening Period Procedures*

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.

3.6.2 *Laboratory Blood Draws, Safety, and Efficacy Assessments*

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).

3.6.3 *ECG Assessments*

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.

3.6.4 *Safety Follow-Up Visit*

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.

4 OUTCOME VARIABLE DEFINITIONS

4.1 Demographic Characteristics

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

4.2 Screening, Qualification, and Baseline Characteristics

Screening:

Inclusion/exclusion criteria, demographic characteristics of age, sex, race, ethnicity, height, weight, body mass index (BMI), medical history, prior and concomitant medications, physical examination, vital signs, adverse events, pregnancy test, 12-lead electrocardiogram (ECG), clinical laboratory results, urine drug screen, alcohol screen, Positive and Negative Syndrome Scale (PANSS), and Columbia-Suicide Severity Rating Scale (C-SSRS) will be collected at screening.

Qualification:

Patients meeting eligibility requirements at the first Screening Visit will undergo an additional in-clinic Qualification Visit during which the following will be collected: eligibility, urine drug screen, alcohol screen, PANSS, C-SSRS, antipsychotic (AP) blood sample, adverse events, and concomitant medications.

Baseline (Day 1 Pre-Dose):

Eligibility, medical history, physical examination, weight, vital signs, 12-lead ECG, pregnancy test, clinical laboratory results, alcohol screen, PANSS, Personal and Social Performance (PSP), Clinical Global Impression-Severity (CGI-S), Schizophrenia Quality of Life Scale (SQLS), C-SSRS, Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS) will be collected prior to dose administration.

4.3 Efficacy Assessments

The effect of study drug will be evaluated using several validated instruments as described below.

4.3.1 *Positive and Negative Syndrome Scale (PANSS)*

The PANSS (Kay et al., 1987) 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.

4.3.2 *Clinical Global Impression-Severity (CGI-S) Score*

The CGI-S rating scale (Guy, 1976) 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. CGI-S scores of zero (not assessed) will be treated as missing.

4.3.3 *Personal and Social Performance Scale (PSP)*

The PSP (Morosini et al., 2000) 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.

4.3.4 *Schizophrenia Quality of Life Scale (SQLS)*

The SQLS (Heinrichs et al., 1984) 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’).

4.4 Efficacy Endpoints

4.4.1 *Primary Endpoints*

The primary efficacy endpoint will be the change in PANSS total score at Week 12 from Baseline (Day 1, prior to dosing).

4.4.2 *Secondary Endpoints*

The secondary endpoints for this study are:

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

4.4.3 *Exploratory Endpoints*

Exploratory efficacy endpoints are:

- Change in PANSS total score at Weeks 2, 4, 8 and 10 from Baseline
- Change in PANSS Positive Symptoms Factor Score (PSFS; items P1-P7) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS Negative Symptoms Factor Score (NSFS; items N1-N7) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in General Psychopathology Symptoms Factor Score (items G1-G16) at Weeks 2, 4, 8, 10 and 12 from baseline
- Change in PANSS Cognitive Symptoms (items P2, N5, G5, G10, G11 at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in Marder Negative Symptoms Factor Score (Marder NSFS; items N1, N2, N3, N4, N6, G7, G16) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS total score at Week 12 from the average of the Screening, Qualification, and Day 1 pre-dose assessments
- 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

4.5 Safety and Tolerability Assessments

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.

4.5.1 *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) will be considered an adverse event.

A worsening of the condition under study will not be considered as an AE.

An AE can be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease temporally associated with the Study Medication, whether or not it is related to the product.

4.5.2 *Columbia Suicide Severity Rating Scale*

The Columbia Suicide Severity Rating Scale (C-SSRS, Oquendo et al., 2003) 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 (Baseline/Screening and Since Last Visit).

4.5.3 *Laboratory Safety Assessments*

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Assessments (Table 1).

Alcohol breathalyzer:	Assesses ethyl alcohol
Coagulation:	Includes prothrombin time test (PT), partial prothrombin time test (aPTT), international normalized ratio (INR)
Hematology:	Consists of complete blood count, platelet count, white blood cell count with differential
Pregnancy:	Assesses hCG; conducted for females of childbearing potential only
Serum renal parameters:	Includes blood urea nitrogen (BUN), serum creatinine, eGFR
Serology screen:	Includes human immunodeficiency virus antibody (HIV-Ab), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV-Ab)
Serum chemistry:	Includes 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
Urinalysis:	Includes bilirubin, glucose, ketones, nitrates, occult blood, protein, specific gravity, urobilinogen, pH, leukocytes, microscopy, creatinine, UACR, urine volume

Urine drug screen:	Includes amphetamines/methamphetamines, barbiturates, benzodiazepines*, cocaine metabolites, methadone, phencyclidine, opiates

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

4.5.4 *Vital Signs*

Resting vital signs, including systolic, diastolic blood pressure, heart rate (measured as pulse), respiratory rate and temperature will be measured after the patient has been in a supine or semi-supine position for at least 5 minutes at the time points specified in the schedule of events (Table 1).

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.

4.5.5 *Electrocardiogram*

Twelve-lead electrocardiograms (ECGs) 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. ECG will be performed at Screening, Baseline, Week 6, and Week 12; if Week 6 visit is a remote visit, ECG assessment may be performed at Week 8 or 10).

4.5.6 *Physical Examination*

A full physical examination will be performed at Screening, Baseline, and Week 12. It will include an examination of all major organ systems. Brief physical examinations will be symptom-directed and performed at Weeks 2, 4, 6, 8, 10, and 13 (follow-up); the Week 13 brief physical exam will be conducted if the visit occurs in-clinic.

4.6 Extrapyramidal Symptoms

4.6.1 *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.

4.6.2 *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.

4.6.3 *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, 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.

4.7 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 of the protocol will be required for patients to be eligible for randomization to the Treatment Period.

4.8 CTP-692 Blood Level

CTP-692 blood levels will be analyzed and reported separately by the bioanalytical laboratory. Times of blood draws relative to dosing of Study Medication will be provided in a listing.

4.9 Concomitant Medications

Concomitant medications will be reviewed and documented each visit during the study and are defined as any medications received at or after the first dose of study medication, medication that was received before initial dosing and continued after initial dosing of study medication, or medication with missing stop date.

4.10 Prior Medications

Prior medications are any medications that ended before the first dose of study medication.

5 STATISTICAL ANALYSES

Statistical analyses will be performed using SAS® software version 9.4.

5.1 Statistical Methodology

5.1.1 *Sample Size Determination*

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 level.

5.1.2 *Populations for Statistical Analysis*

5.1.2.1 Safety Population

The Safety Population (SP) includes all patients who receive at least one dose of study medication.

5.1.2.2 Efficacy Population

The Efficacy Population (EP) will include all patients who receive Study Medication and have at least one post-baseline PANSS assessment during the Treatment Period.

5.1.2.3 Efficacy Population – COVID Related

Due to the pandemic during the conduct of the trial, a COVID-related Efficacy Population (COVID-EP) will also be identified. COVID-EP will be defined as all patients who receive study medication and have at least one post-baseline PANSS assessment during the Treatment Period and have not discontinued from the study or had a dose interruption due to direct COVID-related events. The COVID-related Efficacy Population will be identified prior to database lock and will exclude individuals who contracted the virus, had clinic access restricted due to COVID conditions, etc.

5.1.2.4 Per-Protocol Population

The Per Protocol analysis population (PP) will include all patients in the Efficacy Population who were dosed according to protocol with no major protocol deviations with respect to eligibility criteria and efficacy assessments, and will be finalized prior to database lock.

The full set of efficacy analyses will be conducted for the EP and COVID-EP, whereas analyses for the PP analysis population will be restricted to the change in PANSS Total Score at weeks 2, 4, 8, 10, and 12.

Individual assignment to each analysis population will be provided in a listing.

5.1.2.5 Subjects Enrolled More Than Once

In the event subjects are found to have enrolled (been randomized and treated) more than once within the study, the first enrollment will be designated as the

primary enrollment. Only the primary enrollment will be included in efficacy analyses. Safety data from additional enrollments will generally be included in analyses, depending on analysis type and treatments received.

5.1.3 *Statistical Analyses – General Considerations*

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.

The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and standard deviation.

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment. Baseline is defined as the last observation prior to initiation of Study Medication.

Listings for CSR Appendix 16.2 will include all the patient data points being collected or derived for analyses. Data listings will be provided for all patients up to the point of study completion or withdrawal.

All statistical tests will be 2-sided with a significance value of 0.05. Patients will be summarized by randomized treatment group, except for the Safety Population, which will be summarized by actual treatment received. There will be no adjustments for multiple comparisons.

5.1.4 *Procedures for Handling Missing Data*

In general, missing data will not be imputed, as the Mixed Model Repeated Measures (primary analysis approach) is considered valid under a Missing at Random (MAR) missingness mechanism.

As a sensitivity analysis for the primary endpoint, 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.

A listing will be provided indicating patients and visits with missing data or remote visits due to COVID-19, as well as early terminations due to COVID-19.

5.1.5 *Study Day and Visit Window Definitions*

The baseline assessment for all efficacy endpoints is defined as last assessment prior to the first dose of Study Medication on Day 1. Data obtained during unscheduled and at the Week 12/Early Termination early visits will be allocated to the scheduled time point corresponding to the visit window in which they fall in as specified in Table 2. For patients completing the study, data will be analyzed based on the nominal visits and nominal time points. If the data from the nominal visit or time point are missing or the patient did not complete the study, data from

unscheduled visits or the Week 12/Early Termination visit within the time interval for the same nominal visit or time point will be used. If multiple visits among unscheduled or Early Termination assessments fall in the same visit window or time point, the non-missing assessment closest to target time point will be selected for analysis. If multiple values are the same number of days away from the target study day, then the latter value will be used. In the unlikely event an unscheduled or Early Termination visit, associated with a particular visit window, falls either prior to the actual previous nominal visit date or after the subsequent nominal visit date, it will not be used. This is done simply to ensure the data assigned to particular analysis time points will not be out of sequence.

The first date on which patient received the Study Medication will be used as the Study Day 1. Study days for other visits will be calculated as follows:

- Before Study Day 1 visit: Study Day = date of assessment – date of Study Day 1
- On or after Study Day 1 visit: Study Day = date of assessment – date of Study Day 1 + 1

Last study date is the last visit date of any scheduled, unscheduled, or Early Termination visits. Last Study Day is calculated as:

- Last Study Day = last study date – date of Study Day 1 + 1

The target study days of Study Center Visits are summarized below.

Table 2 – Guidelines for Assigning Unscheduled and Early Termination Visits for Efficacy Assessments

Week/Visit	Time Interval (Day)	Target Time Point (Day)
-5/Screening	Use nominal	-35*
-3/Qualification	Use nominal	-24 to -21*
1 (Baseline/Day 1)	Last assessment prior to dosing	1
2	8 to 21	14
4	22 to 35	28
6	36 to 49	42

8	50 to 63	56
10	64 to 77	70
12	78 to 1 day prior to Safety Follow-up	84
13/Safety Follow-up	Use nominal	91

*5-week Screening/Qualification Period may be extended up to 2 weeks if repeat laboratory test results for confirmation of eligibility are pending.

5.2 Screening and Baseline Characteristics

Summary tables will be constructed for the following screening or pre-dose data and summarized by treatment group: demographic characteristics of age, sex, race, ethnicity, weight, height and body mass index (BMI), medical history, prior and concomitant medications, laboratory examinations, vital signs, and ECG for the safety population.

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1 September 2020) terminology. Prior and concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term (September 2020 version). Medical history and prior and concomitant medications will be summarized for the Safety Population.

Listings will be provided for eligibility criteria violations, demographics, medical history, and prior and concomitant medications.

5.3 Patient Disposition

The number and percentage of patients in each treatment group will be summarized for each investigative site (and combined) for each analysis population. The number and percentage of patients who are randomized, treated, prematurely discontinued (overall and by reason), and who complete the study will be summarized. The frequency and percentage of patients who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment. Individual patient dispositions will be provided by a listing.

All reported major protocol deviations and determined exclusions from any analysis population(s) will be provided in a listing.

5.4 Efficacy Analyses

5.4.1 *Primary Analysis*

The primary efficacy endpoint will be the change in PANSS total score at Week 12 from Baseline. A mixed model for repeated measures (MMRM) will be used to

assess treatment group differences for change from baseline. Fixed effects will include treatment group, analysis visit, treatment-by-visit interaction, and a baseline-by-visit interaction. Visit will be fit as a repeated effect using the repeated statement in SAS. The baseline score will be included as a continuous covariate. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a Toeplitz structure will be used.

Least squares means will be presented for treatment*visit, with the significance level of the treatment-by-visit interaction presented in summary tables. Pair-wise comparisons of differences in LS means, two-sided 95% confidence intervals (CIs) on differences, and p-values will be provided for each active treatment versus placebo for each visit.

A listing for PANSS individual questions as well as subscale totals will be provided.

5.4.2 *Secondary Analyses*

Change in CGI-S score and PSP score at Week 12 from Baseline will be evaluated as secondary endpoints.

MMRM analyses, as described for the primary analysis, will be conducted on the change scores for the CGI-S and PSP. Individual patient scores for the CGI-S and PSP will be provided in listings.

5.4.3 *Exploratory Analyses*

The following exploratory analyses will be conducted using MMRM as specified above:

- Change in PANSS total score at Weeks 2, 4, 8 and 10 from Baseline
- Change in PANSS Positive Symptoms Factor Score (PSFS; items P1-P7) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS Negative Symptoms Factor Score (NSFS; items N1-N7) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in General Psychopathology Symptoms Factor Score (items G1-G16) at Weeks 2, 4, 8, 10 and 12 from baseline
- Change in PANSS Cognitive Symptoms (items P2, N5, G5, G10, G11) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in Marder Negative Symptoms Factor Score (Marder NSFS; items N1, N2, N3, N4, N6, G7, G16) at Weeks 2, 4, 8, 10, and 12 from Baseline
- Change in PANSS total score at Week 12 from the average of the Screening, Qualification, and Day 1 pre-dose assessments
- 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

5.5 Safety Analyses

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 (AEs) will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA version 23.1 coding system 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.

5.5.1 *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. These will be listed. 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. Individual patient TEAEs will be provided in a listing.

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 severity (mild, moderate, severe) as well as relationship to Study Medication (possibly, probably, or definitely related, unlikely 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.

A summary of adverse events will be provided in a table and will include numbers of subjects and percentages for following:

- Total TEAEs in each treatment group
- Number of patients with TEAEs
- Moderate or severe TEAEs (Grade 2 or above)
- Any related TEAE
- TEAEs leading to discontinuation
- Total SAEs
- Max severity of SAEs
- Any related SAE
- SAEs leading to discontinuation
- SAEs leading to death

Treatment-emergent adverse events that result in dose interruption (with subsequent resumption of dose) will also be identified.

5.5.2 *Columbia Suicide Severity Rating Scale*

The C-SSRS data will be summarized descriptively. Individual patient data will be provided in a listing. 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

5.5.3 *Clinical Laboratory Evaluations*

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. The tables will also include changes from Baseline. Individual patient listings will be provided.

5.5.4 *Physical Examination*

A listing of physical examination findings will be provided by patient. Pregnancy, alcohol screening, and drug testing results will be provided by patient.

5.5.5 *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. Individual patient listings will be provided.

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

5.5.6 *12-Lead 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. A table presenting frequencies and percentages of ECG findings described as “abnormal, clinically significant,” “abnormal, not clinically significant,” and “normal” will be provided by treatment group.

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

>30 msec increase

>60 msec increase

5.5.7 *Extrapyramidal Symptoms*
Scores on the SAS, AIMS, and BARS will be summarized for each corresponding visit. Individual patient scores will be listed.

5.5.8 *Antipsychotic Medication Blood Level*
The presence (Yes/No) of antipsychotic medications in the blood at the Qualification Visit will be provided per patient as a listing.

5.5.9 *CTP-692 Blood Level*
A listing indicating the time of CTP-692 blood draw relative to time of dose will be provided per patient.

5.5.10 *Concomitant Medications*
Concomitant medications will be summarized (n and %) by ATC class and preferred term (coded by WHODrug coding dictionary version B3 September 2020) for each treatment group. This table will also include an overall total column. Concomitant medications for individual patients will be provided in a listing. A separate table for concomitant antipsychotic medications will also be provided.

5.6 Study Medication Exposure
The number of days of Study Medication administration will be summarized for each treatment group, as well as provided in a listing per patient.

5.7 Interim Analyses
No interim analyses are planned for this study.

6 REFERENCES

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7 TABLES, LISTINGS AND FIGURES

A separate document containing the list of tables, listings, and figures (TFLs) to be included in the post-text Appendix 14 of the CSR will be provided. TFLs may be modified with Sponsor's approval and as deemed necessary without update to the SAP.