Phase II, Double-blind, Randomized, Placebo-controlled, Parallel-group, Trial to Explore Efficacy, Safety and Pharmacokinetics of CPL500036 (PDE10A inhibitor) in Patients With an Acute Exacerbation of Schizophrenia

02PDE2019

Statistical Analysis Plan

Protocol version number and date:	Version 4.0 16 MAY 2024
Protocol Number:	02PDE2019
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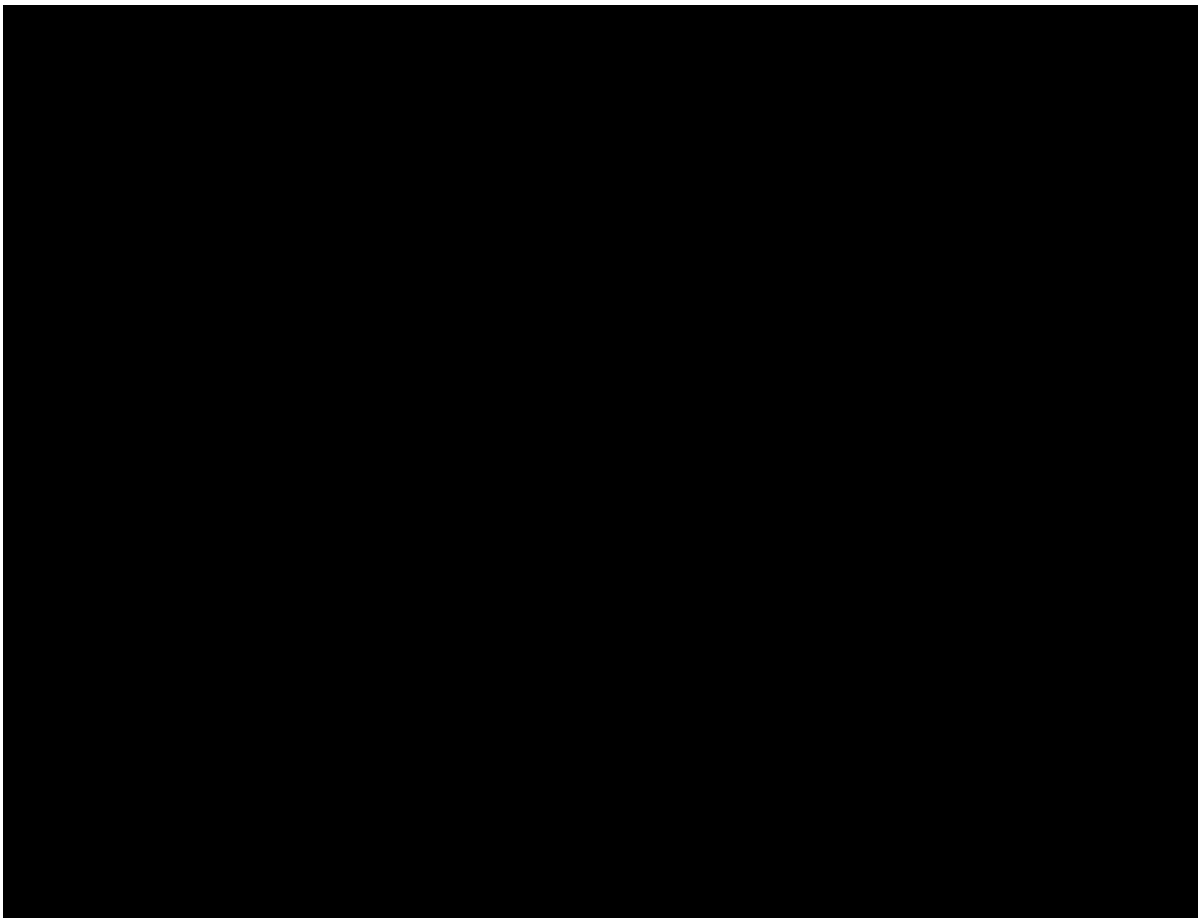
Data management:	
Data Management: Contact(s):	
Biostatistics (baseline characteristics, primary and secondary endpoint analyses, safety analyses, PD analyses)	
Biostatistics (PK and exploratory analyses)	

Summary of Changes



Signatures

Author:

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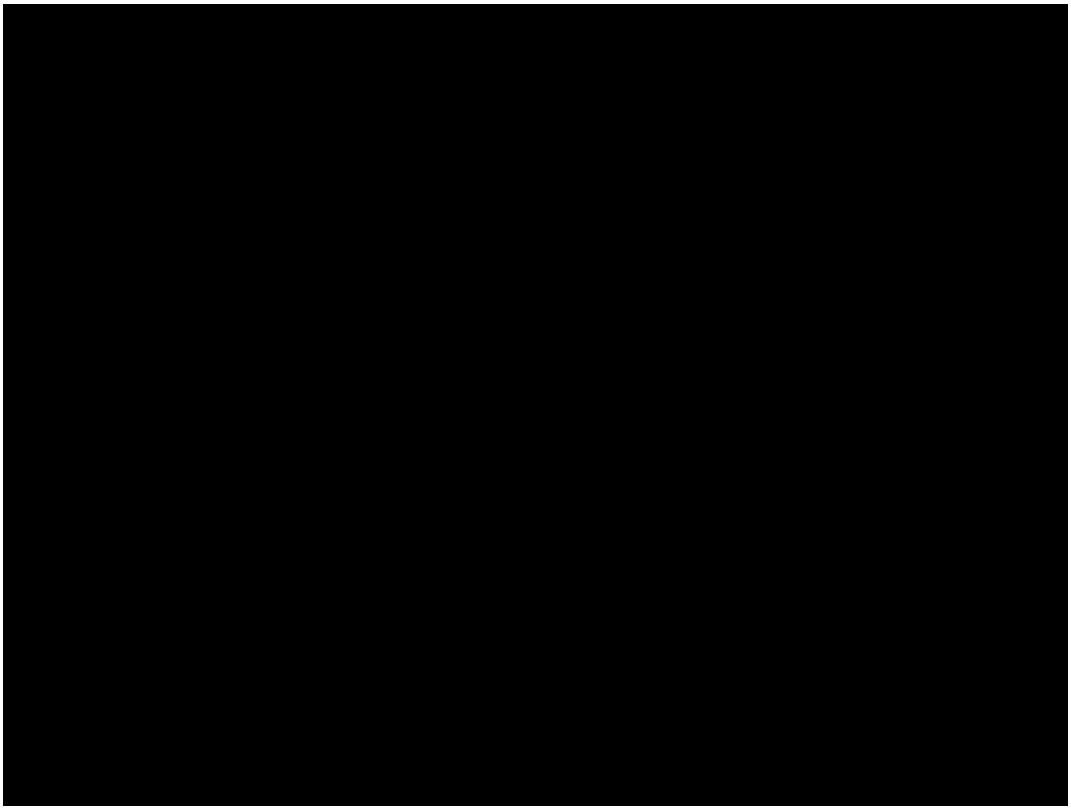

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
AUC	area under the curve
BACS	Brief Assessment of Cognition in Schizophrenia
$AUC_{(0\text{-}inf)}$	Area under plasma concentration-time curve from time zero extrapolated to infinity
$AUC_{(0\text{-}tau)}$	Area under plasma concentration-time in the dosing interval, i.e. from time zero to exactly 24 hours
$AUC_{(0\text{-}24h)}$	Area under plasma concentration-time curve from time zero to 24 hours measured or extrapolated to the actual sampling time (referred as $AUC_{0\text{-}24}$ in Clinical Study Protocol)
BMI	Body Mass Index
CGI-I	Clinical Global Impression Scale – Improvement
CGI-S	Clinical Global Impression – Severity
CL/F	apparent clearance
C_{max}	maximum observed concentration
C_{trough}	Observed trough concentrations
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
D	dose
ECG	electrocardiogram
(e)CRF	(electronic) Case Report Form
ESRS	Extrapyramidal Symptom Rating Scale
F	Bioavailability
FAS	Full Analysis Set
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
K_{el}	elimination rate constant

MedDRA	Medical Dictionary for Regulatory Activities
NA	not available
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol population
PS	Pharmacokinetic Set
PSPC	Pharmacokinetic Set for parameter calculation
PT	preferred term
SAE	serious adverse event
SS	safety set population
SD	standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	half-life
t_{max}	Time corresponding to occurrence of C_{max}, i.e. the time after administration of a drug when the C_{max} is reached
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
V_z/F	apparent volume of distribution during terminal phase
WHO	World Health Organization

1. Introduction

This statistical analysis plan reflects study protocol 02PDE2019 version 4.0, dated 16-May-2024. It follows the principles of the Guidelines ICH E3 and ICH E9.

All aspects of the statistical analysis shall be covered by this document. It provides a technical and detailed description of handling the collected data and statistical methods deployed.

1.1. SOPs to be followed

The statistical analysis will be carried out according to [redacted] SOPs. The statistical report will be written according to the ICH Guidelines.

2. Overview of the protocol

2.1. Objectives of the study

2.1.1. Primary objective

Primary objective: to determine if CPL500036 administered for 28 days can attenuate the positive symptoms associated with schizophrenia.

2.1.2. Secondary objectives

2.1.2.1. Efficacy:

- To determine if CPL500036 administered for 28 days can attenuate the negative symptoms associated with schizophrenia.
- To determine if CPL500036 administered for 28 days results in overall clinical improvement as assessed by the Clinical Global Impression Scale - Improvement (CGI-I).
- To determine if CPL500036 administered for 28 days results in overall clinical improvement as assessed by the Positive and Negative Symptom Scale (PANSS).

2.1.2.2. Safety:

- To assess the safety and tolerability of CPL500036 administered for 28 days.

2.1.2.3. Pharmacokinetics

- To assess the pharmacokinetic (PK) profile of CPL500036 administered for 28 days.

2.2. Endpoints

2.2.1. Primary endpoints

Primary endpoint:

- Change from baseline in PANSS positive subscale at Week 4.

2.2.2. Secondary endpoints

2.2.2.1. Efficacy:

- Change from baseline in PANSS positive subscale at Week 1, 2 and 3 [Time Frame: Weeks 1, 2, and 3].
- Change from baseline in PANSS Total Score at Weeks 1, 2, 3, 4 [Time Frame: Weeks 1, 2, 3, and 4].
- Change from Baseline in PANSS Subscales Using the Marder 5-factor Model at Weeks 1, 2, 3, and 4 [Time Frame: Weeks 1, 2, 3, and 4].
- Change from Baseline in PANSS Negative Subscales at Weeks 1, 2, 3 and 4 [Time Frame: Weeks 1, 2, 3, 4].
- Change from Baseline in PANSS general psychopathology Subscale at Weeks 1, 2, 3 and 4 [Time Frame: Weeks 1, 2, 3, 4].
- Percentage of Clinical Responders Based on the PANSS Total Score. A clinical responder is defined as a ≥ 30% decrease from baseline, [Time Frame: Weeks 1, 2, 3, 4].
- Change from Baseline in Clinical Global Impression - Severity (CGI-S) Score at Weeks 1, 2, 3, and 4 [Time Frame: Weeks 1, 2, 3, 4].
- Clinical Global Impression Scale - Improvement (CGI-I) Score at Weeks 1, 2, 3, 4 [Time Frame: Weeks 1, 2, 3, 4].
- Percentage of Responders Based on CGI-I Ratings Score at weeks 1, 2, 3, 4. A responder is defined as a rating of 'much improved' or 'very much improved'. [Time Frame: Weeks 1, 2, 3, 4].
- Change from Baseline in Brief Assessment of Cognition in Schizophrenia (BACS) Score at Weeks 2 and 4 [Time Frame: Weeks 2 and 4].

2.2.2.2. Safety:

- Physical, neurological, ophthalmological, and dermatological examination findings.
- Adverse event assessments.
- Hematologic, clinical chemistry, coagulation and urinalysis results.
- Electrocardiogram (ECG) results.
- Extrapyramidal side effects monitoring using the Extrapyramidal Symptom Rating Scale (ESRS).

2.2.2.3. Pharmacokinetics

The data permitting the following plasma PK parameters will be evaluated after single and multiple dose administration for the extensive and sparse PK sampling groups:

- Maximum observed concentration (C_{max})
- Time corresponding to occurrence of C_{max} (t_{max})
- AUC from time zero to 24 hours ($AUC_{(0-24h)}$)
- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution during terminal phase (Vz/F)
- Concentration immediately prior to dosing (C_{trough}). This parameter will only be calculated during the multiple dose administration.

Safety endpoints:

2.3. Study design

This is a double-blind, randomized, placebo controlled, parallel group, dose ranging study to explore the efficacy, safety, tolerability, and PK parameters of two different doses of CPL500036 (PDE10A inhibitor) in patients with an acute exacerbation of schizophrenia when administered for 28 days.

The study will be conducted at multiple clinical units. Approximately 165 patients will be randomized at a 1:1:1 ratio to receive 20 mg CPL500036, 40 mg CPL500036 or placebo.

The study will comprise of a Screening Period (that will include a prior Medication Washout Period), a Treatment Period and a Follow-up Period.

For the Screening Period, patients will undergo screening assessments from Day -10 to Day -8 in multiple settings (i.e., emergency departments, outpatient clinics, etc.). Rolling admission will be employed in this study. Patients that fulfil all the inclusion criteria and none of the exclusion criteria will immediately be admitted to the Clinical Unit and enter a Medication Washout Period of up to 7 days (Day -7 to Day -1) before the start of the 28-day Treatment Period. The duration of the Medication Washout Period may be shorter or omitted for non-medicated patients.

During the Treatment Period, patients will be dosed with 20 mg CPL500036, 40 mg CPL500036 or placebo once daily for 28 consecutive days (Day 1 to Day 28). Patients will remain in-house for the duration of the Treatment Period.

Approximately 30% of the patients (17 patients in each of the 3 treatment groups) will undergo extensive PK sampling during the Treatment Period, and the remaining 70% of the patients will only undergo sparse PK sampling.

On Day 29, the patients may resume anti-psychotics treatment. The Investigator will continue to monitor the patient for safety and clinical stability. Patients will be discharged from the Clinical Unit based on local standards of care if the patient is in a stable condition under the regular medication(s).

After discharge from the Clinical Unit, patients will return to the Clinical Unit for 2 once weekly Follow-up Visits, 7 (± 1) and 14 (± 1) days after the last dose of the investigational medicinal product (IMP) (Day 35 and Day 42).

Patients that withdraw or are withdrawn from the study will attend an early termination visit at the Clinical Unit and 2 safety Follow-up Visits 7 (± 1) and 14 (± 1) days after the last dose of IMP.

2.3.1. Inclusion-Exclusion Criteria

2.3.1.1. Inclusion Criteria

Patients eligible for inclusion in this study have to fulfil all of the following criteria:

1. The patient has a primary diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5], 295.90) confirmed by clinical interview (Structured Clinical Interview for DSM-5 Clinical Trial Version [SCID-5-CT]). The participant's initial diagnosis must be greater than or equal to (≥) 2 year before Screening.
2. Male or female patient aged 18 to 65, inclusive, at Screening.
3. The patient's psychotic symptoms were exacerbated within 2 months (60 days) prior

to Screening (e.g., aggravated delusion).

4. The patient has a score of 5 (moderate severe) or higher in 3 or more items of the following PANSS items at Screening and Day -1: delusions (P1), conceptual disorganization (P2), hallucinations (P3), suspiciousness (P6), and unusual thought content (G9).
5. The patient has a PANSS Total Score of 80 or higher during Screening and on Day -1.
6. A female is eligible to participate if she is not pregnant (negative pregnancy test at Screening and Day -1), not breastfeeding, and at least 1 of the following conditions applies:
    a) Not a woman of childbearing potential (a woman is considered to be of non-childbearing potential if she is post-menopausal for at least 12 months or is surgically sterile [hysterectomy, bilateral oophorectomy, tubal ligation]).
    b) Woman of childbearing potential, who agree to use contraceptive methods during the Treatment Period and for at least 28 days after the last dose of the study drug. The following are acceptable contraceptive methods: bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with spermicide; and cap, diaphragm, or sponge with spermicide.
7. Male patients must agree to use a barrier method of contraceptive (condom + spermicide gel) for at least 90 days after the last dose of the study drug.
8. The patient has a Clinical Global Impression Scale- Severity of Illness Scale (CGI-S) of 4 or greater at Screening and Day -1.
9. The patient is able to and agrees to remain off prior antipsychotic medication and all excluded medications as outlined in the protocol for the duration of the Treatment Period.
10. The patient is able to sign informed consent after receiving information about the trial.
11. The patient has the ability and willingness to comply with the requirements and restrictions of the study protocol.

2.3.1.2. Exclusion Criteria

Patients eligible for inclusion in this study must not fulfil any of the following criteria:

1. The patient has a decrease in the PANSS Total Score by 20 percent (%) or more at Baseline (Day -1) compared with the Total Score at Screening ([PANSS Total Score at Screening - PANSS Total Score at Baseline]/[PANSS Total Score at Screening-30)]*100 ≥ 20%).
2. Patient participated in another interventional clinical study with an IMP during the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug.
3. The patient has uncontrolled, hypertension, hypotension, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the patient to participate or potentially confound the study results.
4. The patient has a history of severe head injury, traumatic brain injury, myocardial infarction or stroke.
5. The patient has a positive urine drug result (illicit, illegal or without valid prescription or medical need) at Screening.
6. The patient has a moderate or severe substance use disorder (meeting more than 4 diagnostic criteria of DSM-5 either currently or within the last 6 months) for alcohol or other substances of abuse except nicotine or caffeine.
7. If female, the patient is pregnant (a positive pregnancy test at Screening or Day -1) or lactating or intending to become pregnant or intending to donate ova, before or during the course of the study or within 12 weeks after the last dose.

8. The patient has a history of or known personality disorder or other psychiatric disorder that, in the opinion of the Investigator, would interfere with participation in the study.
9. The patient has a history of neuroleptic malignant syndrome, water intoxication, or paralytic ileus or other conditions that may interfere with absorption of study drug.
10. The patient is considered by the Investigator to be at imminent risk of suicide or injury to self, others, or property or participants who within the past year prior to Screening have attempted suicide or have positive answers on item 4 or 5 on the C-SSRS at Screening or on Day -1.
11. The patient has Parkinson's disease, tardive dyskinesia, or other chronic movement disorder that may interfere with the interpretation of study results.
12. The patient has any existing or previous history of cancer that has been in remission for less than 5 years prior to Screening.
    Note: this criterion does not include those participants with basal cell, stage I squamous cell skin cancer or in situ cervical cancer.
13. The patient has newly diagnosed diabetes or requires insulin for their treatment; diabetic patients that have had changes to their diabetic treatment regimen within 30 days prior to Screening or diabetic patients that have been hospitalized for their diabetes and/or diabetes related conditions in the past year prior to Screening.
14. The patient has long QT syndrome or is under treatment with Class 1A (e.g., quinidine, procainamide) or Class 3 (e.g., amiodarone, sotalol) anti-arrhythmic drugs.
15. The patient with acute or chronic hepatitis B or C infection (positive test for hepatitis B surface antigen; positive hepatitis C antibody), known human immunodeficiency virus (HIV) infection, or other acute or ongoing clinically significant viral or bacterial infections.
16. The patient has received any depot preparation (sustained-release formulation) of antipsychotic drugs within 1 month (30 days) prior to Screening.
17. The patient is considered to be treatment resistant. Treatment resistance is defined as prior non-response to 2 courses of treatment with anti-psychotics of different chemical classes for at least 4 weeks each at doses considered to be effective.
18. The patient has received monoamine oxidase (MAO) inhibitors or fluoxetine within 1 month (30 days) before Screening.
19. The patient has received electroconvulsive therapy within 6 months (180 days) before Screening.
20. The patient has 1 or more laboratory values outside the normal range that are considered by the Investigator to be clinically significant at Screening; or has any of the following at Screening:
    - A serum creatinine value > 1.5 times the upper limit of normal (ULN).
    - A total serum total bilirubin value > 1.5*ULN.
    - A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value > 2*ULN.

2.3.2. Randomization and blinding

Both subjects and investigators will be blinded to treatment assignment using IWRS system. A computer-generated randomization schedule prepared by [redacted] prior to study initiation will be used. The randomization will be balanced by using randomly permuted blocks of variable length and will be stratified by PANSS score at Baseline (Day -1) (with two categories: low <95, high ≥95). Investigator will be able to break the blind for a given subject, in case of emergency, using tool provided within eCRF.

2.3.3. Study assessments

Table 1. Schedule of assessments

	Screening Period [a] and Washout Period [b]	Baseline and Washout [b]	Randomization[b]	Treatment Period							
Study Week				**Week 1**			**Week 2**		**Week 3**		
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**2**
Study Plan											
Informed consent	X										
Inclusion/exclusion criteria	X	X	X								
Demographic data	X										
Medical history	X										
Alcohol test and urinary drug screen	X	X									
Viral serology	X										
Weight and height	X	X									
IMP Administration:											
Medication Washout	X	X									
Randomization			X								
CPL500036/Placebo				X	X	X	X	X	X	X	

	Screening Period [a] and Washout Period [b]	Baseline and Washout [b]	Randomization[b]	Treatment Period							
Study Week				**Week 1**			**Week 2**		**Week 3**		
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**2**
Study Plan											
Resumption of anti-psychotics											
Safety and Tolerability:											
Adverse event questioning	X	X		X	X	X	X	X	X	X	
ESRS monitoring [d]	X	X		X		X		X		X	
Prior/concomitant medication	X	X		X	X	X	X	X	X	X	
C-SSRS[e]	X	X						X			
Blood pressure, pulse and respiratory rate (supine) and body temperature [f]	X	X		X	X	X		X		X	
12-lead safety ECG [g]	X	X				X		X		X	

	Screening Period [a] and Washout Period [b]	Baseline and Washout [b]	Randomization[b]	Treatment Period							
Study Week				**Week 1**			**Week 2**		**Week 3**		
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**2**
Study Plan											
Clinical laboratory evaluations (clinical chemistry, hematology, coagulation and urinalysis)	X	X		X		X		X		X	
Physical examination	X	X									
Neurological examination	X	X				X[h]		X[h]		X[h]	
Ophthalmological examination	X										
Dermatological examination	X										
Pregnancy testing	X (serum)	X (urine)									
Efficacy											
PANSS	X	X		X[i]		X[i]		X[i]		X[i]	
CGI-S	X	X				X[i]		X[i]		X[i]	
CGI-I						X[i]		X[i]		X[i]	
BACS		X						X[i]			

	Screening Period [a] and Washout Period [b]	Baseline and Washout [b]	Randomization[b]	Treatment Period							
Study Week				**Week 1**			**Week 2**		**Week 3**		
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**2**
Study Plan											
Pharmacokinetics											
Extensive PK blood sample collection				X [j]	X [k]	X [j]					
Sparse PK blood sample collection				X [l]		X [l]					

BACS: Brief Assessment of Cognition in Schizophrenia; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: Electrocardiogra
Scale; CGI-I: Clinical Global Impression Scale - Improvement; CGI-S: Clinical Global Impression Scale - Severity; IMP: Investiga
and Negative Syndrome Scale; PK: Pharmacokinetic(s).

a) Patients will undergo screening procedures over up to 3 days on an in-house basis in multiple settings (i.e., emergency dep
b) Patients that fulfil all the inclusion criteria and none of the exclusion criteria will then be admitted to the Clinical Unit o Period of up to 7 days (Day -7 to Day -1) before the randomization on Day 0. The duration of the Medication Wash non-medicated patients.
c) Patients will be discharged on local standards of care when patient is in a stable condition under the regular medication(s).
d) Extrapyramidal side effects will be monitored, using the ESRS. It will be performed once at Screening (Day -10 to -2); o 14, 21 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (it will be performed after PAN the follow-up visits.
e) C-SSRS will be conducted once at Screening (Day -10 to -2); once at Baseline (Day -1); on Day 14 and Day 28 when star or after 2h post-dose (it will be performed after PANSS, CGI-S, CGI-I, BACS and ESRS); once during the follow-up visit
f) Respiratory rate, body temperature, 3-positional blood pressure and pulse (after 3 minutes lying down; after 3 minute sitti minutes standing) will be taken once at Screening (Day -10 to -2); once at Baseline (Day -1); thrice on Day 1, Days 2-6, IMP administration) and within 5 minutes before or after 1h 45 minutes and 9h post-dose; once during the follow-up visits

g) ECG will be performed once at Screening (Day -10 to -2); once at Baseline (Day -1); on Day 7, 14, 21 and 28 pre-dose (≤ the follow-up visits.

h) Physical, neurological, ophthalmological and dermatological examinations are to be performed not earlier than 5h post-do

i) The efficacy assessment (PANSS) will be performed on Days 1, 7, 14, 21 and 28 when start of ratings is to be within 5 mi performed before any other scale);

   The efficacy assessments (CGI-S and CGI-I, in that exact order) will be performed on Days 7, 14, 21 and 28 when start o after 2h post-dose (after PANSS);

   The BACS assessment will be performed on Days 14 and 28 when start of ratings is to be within 5 minutes before or af CGI-I).

j) For patients undergoing extensive PK sampling, blood samples for PK analysis collected on Day 1 and Day 7 will be collec 24* hours post-dose.

k) For patients undergoing extensive PK sampling, blood samples for PK analysis collected on Days 2 to 6 and Day 28 will post-dose.

   **please note – the sample 24 hours post-dose on Day 1 it is the same sample as pre-dose on Day 2.*

l) For patients undergoing sparse PK sampling, blood samples for PK analysis collected on Day 1 and Day 7 will be collected

m) For patients undergoing sparse PK sampling, blood samples for PK analysis collected on Day 28 will be collected at pre-d

2.4. Sample size

This proof-of-concept study is powered to rule out an effect size of 0.5 or greater for the primary endpoint. With 50 patients per group, the study has 80% power to detect an effect size of 0.5 or greater for 1 of the 2 dose groups, compared to placebo, given a 2-sample t-test, and a 2-sided 10% significance level. Each dose will be compared to placebo, without adjustment for multiplicity so the type-I error will be slightly inflated, however, as this is a proof-of-concept study, the slight inflation is acceptable. Assuming an approximately 10% of patients may drop out, approximately 165 patients will be randomized (55 patients per group).

3. General aspects of the statistical analysis

3.1. Analysis populations

The following populations are to be analyzed:

- Full Analysis Set (FAS): All patients randomized to either CPL500036 or placebo - based on planned treatment regimen irrespective of their compliance to the planned course of treatment (intent-to-treat principle).
- Per Protocol (PP) Set: Patients from the FAS who completed the Treatment Period (Day 28) on study treatment without a major protocol deviation. Protocol deviations will be determined prior to unblinding.
- Safety Analysis Set (SS): All patients who received at least 1 dose of study treatment (either CPL500036 or placebo).
- Pharmacokinetic Set (PS): All patients in the safety set with at least 1 evaluable PK parameter.
- Pharmacokinetic Set for parameter calculation (PSPC): All patients in the safety set with extensive PK sampling that have at least 1 PK parameter evaluable and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of CPL500036.

The FAS will be the primary analysis set used for all efficacy analyses and the PP analysis set will be used for supportive analyses of the primary and secondary efficacy endpoints. Patients will be included in the treatment group they were randomized to. The SS will be used for all safety analyses and patients will be included in the treatment group based on the treatment they actually received.

3.2. Definition of subgroups

Analysis of primary and secondary endpoints will be provided for FAS and PP population by the following subgroups:

- Sex (male, female).
- Baseline (Day -1) PANSS (low <95, high ≥95).

3.3. Protocol deviations

For the allocation of patients to analysis populations, all protocol deviations will be reviewed according to the criteria specified below. A data review plan, which will be finalized prior to the data review meeting, might further specify the criteria. This plan will further specify all data and listings that are needed to review and assess the protocol deviations.

The determination of major and minor protocol deviations will be performed during the data review meeting and documented in the data review meeting minutes, which will be finalized prior to unblinding of the treatment group for the main analysis of data of the double-blind treatment period.

The following protocol violations are defined as major and will thus lead to the exclusion of a patient from the population:

Table 2. Protocol deviations

Number	Major protocol deviation	Reasons for exclusion from PP population
1	No valid assessment of PANSS at day -1 and week 4 (day 28)	X
2	Any violation than may have an impact on PANSS assessment	X
3	Dose or administration of study medication deviates substantially from protocol schedule	X

3.4. Changes from specifications in the protocol

Not applicable.

3.5. Interim analysis

No formal interim analysis is planned.

3.6. Timing of analysis

Baseline characteristic and efficacy analyses will be performed after the last subject completes a 28-day treatment period. All data until the Day 28 visit will be verified and locked before the unblinding. A safety analysis will be performed after all the data, including follow-up visits will be completed, verified and whole database will be locked.

4. Statistical analysis specifications

4.1. General

Due to exploratory nature of the study statistical significance level will be equal to 0.1. Based on provided assumption on the effect size this study is not sufficiently powered to reject the null hypothesis for the primary study endpoint at the more conventional significance level of 0.05. P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

4.1.1. Definitions/derived variables

Unless otherwise specified, baseline is defined as value collected closest but not later than time of the first IMP administration (Day 1). Values for following forms will be used as baseline:

- PANSS on Baseline (Day -1),

- CGI-S on Baseline (Day -1),
- BACS on Baseline (Day -1),
- ESRS on Baseline (Day -1),
- Vital signs – pre dose (before IMP administration on Day 1),
- Clinical laboratory data (hematology, biochemistry, urinalysis, coagulation) on Day 1,
- 12-Lead ECG on Baseline (Day -1),
- PK blood sample collection [predose] on Day 1.

4.1.1.1. Day 1 and relative study days

Day 1 is defined as the day of the first administration of study medication (reference date). Reference date will include actual time of IMP administration. In general, any date provided in patient listings will be presented as study day (in addition to the date provided): If a date is later than the reference date then the study day is calculated as:

study day = date - reference date +1.

If a date is prior the reference date then the study day is a negative number calculated as

day = date - reference date.

Where applicable (such as classification of pre- vs concomitant medications) fractional part of the study day (i.e. including both date and time) will be used. Otherwise study days will be presented as integers.

4.1.1.2. BMI

BMI is calculated according to the equation:

$$\text{BMI} = \text{weight [kg]} / \text{height [m]}^2$$

BMI will be subsequently categorized using following ranges:

<18.5 – Underweight

<18.5 – 25) – Normal weight

<25 – 30) – Overweight

≥30 – Obese.

4.1.1.3. Duration of disease

Duration of disease will be calculated as:

Duration of disease = (date of signature of ICF – date of initial diagnosis)/365.25,

where ICF is Informed Consent Form.

For partial dates imputation described in section 4.1.5 will be used prior to duration calculation.

4.1.1.4. Duration of current exacerbation

Duration of current exacerbation will be calculated as:

Duration of current exacerbation = date of signature of ICF – start date of current exacerbation,

where ICF is Informed Consent Form.

For partial dates imputation described in section 4.1.5 will be used prior to duration calculation.

4.1.1.5. Treatment exposure and treatment compliance

Exposure to IMP will be calculated as:

Exposure = (Date of last IMP dose – Date of the first IMP dose) + 1

Extent of exposure will be calculated as a sum of exposures of all patients and expressed in patient-treatment years:

Extent of exposure [patient years] = sum(Exposure)/365.25.

4.1.1.6. Drug adherence

A subject is considered as a complier with dosing regimen when at least 80% (that is 23 out of 28 planned doses) of the IMP are compliant - meaning that patient took a full dose consisting of four capsules.
Drug adherence is defined as a number of capsules consumed divided by 112 (4 capsules per day in 28 days) or 4 multiplied by the number of days subject is in the study during the active period (if early terminated).

4.1.1.7. Positive and Negative Syndrome Scale (PANSS)

The PANSS is a 30-item scale used to measure symptoms of schizophrenia. The scale has 7 positive symptom items, 7 negative symptom items, and 16 general psychopathology symptom items. Each item is scored on a 7-point scale by the clinical rater based on a clinical interview with the patient. The efficacy assessment (PANSS) will be performed once at Screening; Baseline; on Days 1, 7, 14, 21 (before any other scale). Results of PANSS are calculated directly in the eCRF according to the formulas:

- Positive score: P1 + P2 + P3 + P4 + P5 + P6 + P7
- Negative score: N1 + N2 + N3 + N4 + N5 + N6 + N7
- Composite score: Positive score – Negative score
- General: G1 + G2 + G3 + G4 + G5 + G6 + G7 + G8 + G9 + G10 + G11 + G12 + G13 + G14 + G15 + G16
- Anergia: N1 + N2 + G7 + G10
- Thought Disturbance: P2 + P3 + P5 + G9
- Activation: P4 + G4 + G5
- Paranoid/Belligerence: P6 + P7 + G8
- Depression: G1 + G2 + G3 + G6
- Supplemental: P4 + P7 + G6 + S1 + S2 + S3
- Total score: Positive score + Negative score + General score

Where P = POSITIVE, N = NEGATIVE, G = GENERAL, S = SUPPLEMENTAL subsection of PANSS questionnaire.

Disease activity will be measured by PANSS Total Score and classified as low (PANSS <95) and high (PANSS >= 95).

Assessment of clinical responder will be performed based on the PANSS Total Score and is defined as a >= 30% decrease from baseline and calculated from the formula:

*PANSS decrease = (PANSS at week X – PANSS at baseline)/(PANSS at baseline -30) * (-100%).*

The adjustment of -30 points is due to the fact that PANSS total score ranges from 30 to 210 points. When unadjusted scores are used to calculate percentage change from baseline, it results in lower values of the percentage change, thus underestimating the response to the treatment and decreasing the proportion of responders (Leucht et al 2010).

4.1.1.7.1. Marder 5-factor model

For further analysis PANSS items will be used to create 5 new scores according to Marder 5-factor model (Hopkins, S.C., et al., 2018):

- Positive score = P1 + P3 + P5 + P6 + N7 + G1 + G9 + G12
- Negative score = N1 + N2 + N3 + N4 + N6 + G7 + G16
- Disorganized thoughts = P2 + N5 + G5 + G10 + G11 + G13 + G15
- Uncontrolled hostility/excitement = P4 + P7 + G8 + G14
- Anxiety/depression = G2 + G3 + G4 + G6

Where P = POSITIVE, N = NEGATIVE, G = GENERAL subsection of PANSS questionnaire.

4.1.1.8. Clinical Global Impression Scale – Severity (CGI-S)

The Clinical Global Impression (CGI) Scale is a standardized assessment tool that the Investigator can use to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI Scale consists of 3 global subscales formatted for use with the Global Scoring Sheet. The first subscale, Severity of Illness, assesses the Investigator's impression of the patient's current illness state. Scores on the Severity of Illness subscale range from 1 = not ill at all to 7 = among the most extremely ill. The efficacy assessment (CGI-S) will be performed once at Screening; Baseline; on Days 7, 14, 21 and 28 (after PANSS). Result of CGI-S will be analyzed numerically.

4.1.1.9. Clinical Global Impression Scale – Improvement (CGI-I)

Clinical Global Impression Scale - Improvement is a 7 points scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. CGI-I will be performed on Days 7, 14, 21 and 28 (after PANSS and CGI-S). Result of CGI-S will be analyzed numerically.

Subject is to be considered as responder when rating is 1 = very much improved or 2 = much improved. Percentage of responders will also be shown.

4.1.1.10. Brief Assessment of Cognition in Schizophrenia (BACS)

The Brief Assessment of Cognition in Schizophrenia (BACS) is specifically designed to measure treatment-related improvements in cognition and includes alternate forms. BACS is a reliable and sensitive measure of cognitive function in schizophrenia. The BACS is a cognition assessment battery that assesses 6 domains of cognitive function found to be consistently impaired in schizophrenia: verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency. Brief Assessment of Cognition in Schizophrenia will be performed at Baseline and on Days 14 and 28 (after PANSS, CGI-S and CGI-I). Raw scores are transferred to VeraSci where results are converted to T-Scores and based on that composite score is calculated and later transferred back according to the Data Transfer Agreement.

4.1.1.11. Extrapyramidal Symptom Rating Scale (ESRS)

The Extrapyramidal Symptom Rating Scale (ESRS) was developed to assess four types of drug-induced movement disorders (DIMD): Pakinsonism, akathisia, dystonia and tardive

dyskinesia (TD). It will be performed once at Screening (Day -10 to -2); once at Baseline (Day -1), once on Day 1, 7, 14, 21 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (it will be performed after PANSS, CGI-S, CGI-I and BACS); once during the follow-up visits. A baseline assessment will be performed at Day -1 and repeated on days 7, 14, 21, 28 and follow-up visits. The ESRS consists of four subscales and four CGI-S scales:

- A questionnaire of EPS or DIMD (part I),
- An examination of Parkinsonism and akathisia (part II),
- An examination of dystonia (part III),
- An examination of dyskinesia (part IV),
- Clinical global impression severity (CGI-S) scales of tardive dyskinesia, Parkinsonism, dystonia and akathisia (part V – part VIII).

Total score for DIMD (Chouinard, G., Margolese, H.C., 2005) is formed based on all 41 items of the ESRS (part I – part IV), while CGI-S's are analyzed as separate items (part V – part VIII).

For the subjective examination (subscale I of the ESRS) scoring is on a 4-point scale (from 0 to 3). Rest of the DIMD examination (part II – part IV) is scored on a 7-point scale (from 0 to 6). Total score for DIMD is sum of the all 41 items from part I to part IV. For more details about scoring please refer to the table below.

Table 3. ESRS scoring

ESRS Part	Symptom	Scoring
Part I		Absent = 0 Mild = 1 Moderate = 2 Severe = 3
Part II	Tremor	None = 0 Borderline, occasional = 1 Small amplitude, occasional = 2 Small amplitude, frequent = 3 Small amplitude, constant or almost so = 4 Moderate amplitude, occasional = 3 Moderate amplitude, frequent = 4 Moderate amplitude, constant or almost so = 5 Large amplitude, occasional = 4 Large amplitude, frequent = 5 Large amplitude, constant or almost so = 6
	Bradykinesia	Normal = 0 Global impression of slowness in movements = 1 Definite slowness in movements = 2 Very mild difficulty in initiating movements = 3 Mild to moderate difficulty in initiating movements = 4 Difficulty in starting or stopping any movement, or freezing on initiating voluntary act = 5 Rare voluntary movement, almost completely immobile = 6
	Gait and Posture	Normal = 0 Mild decrease of pendular arm movement = 1 Moderate decrease of pendular arm movement, normal steps = 2 No pendular arm movement, head flexed, steps more or less normal = 3 Stiff posture (neck, back) small step (shuffling gait) = 4 More marked, festination or freezing on turning = 5 Triple flexion, barely able to walk = 6
	Postural Stability	Normal = 0 Hesitation when pushed but no retropulsion = 1 Retropulsion but recovers unaided = 2 Exaggerated retropulsion without falling = 3 Absence of postural response would fall if not caught by examiner = 4 Unstable while standing, even without pushing = 5 Unable to stand without assistance = 6
	Rigidity	Normal muscle tone = 0 Very mild, barely perceptible = 1

ESRS Part	Symptom	Scoring
		Mild (some resistance to passive movements) = 2 Moderate (definite difficulty to move the limb) = 3 Moderately severe (moderate resistance but still easy to move limb) = 4 Severe (marked resistance with definite difficulty to move the limb) = 5 Extremely severe (limb nearly frozen) = 6
	Expressive Automatic Movements	Normal = 0 Very mild decrease in facial expressiveness = 1 Mild decrease in facial expressiveness = 2 Rare spontaneous smile, decrease blinking, voice slightly monotonous = 3 No spontaneous smile, staring gaze, low monotonous speech, mumbling = 4 Marked facial mask, unable to frown, slurred speech = 5 Extremely severe facial mask with unintelligible speech = 6
	Akathisia	Absent = 0 Looks restless, nervous, impatient, uncomfortable = 1 Needs to move at least one extremity = 2 Often needs to move one extremity or to change position = 3 Moves one extremity almost constantly if sitting, or stamps feet while standing = 4 Unable to sit down for more than a short period of time = 5 Moves or walks constantly = 6
Part III		Absent = 0 Very mild = 1 Mild = 2 Moderate = 3 Moderately severe = 4 Severe = 5 Extremely severe = 6
Part IV	Lingual movements	None = 0 Borderline = 1 Clearly present, within oral cavity, occasional = 2 Clearly present, within oral cavity, frequent = 3 Clearly present, within oral cavity, constant or almost so = 4 With occasional partial protrusion, occasional = 3 With occasional partial protrusion, frequent = 4 With occasional partial protrusion, constant or almost so = 5 With complete protrusion, occasional = 4 With complete protrusion, frequent = 5 With complete protrusion, constant or almost so = 6
	Jaw movements	None = 0 Borderline = 1 Clearly present, small amplitude, occasional = 2 Clearly present, small amplitude, frequent = 3 Clearly present, small amplitude, constant or almost so = 4 Moderate amplitude, but without mouth opening, occasional = 3 Moderate amplitude, but without mouth opening, frequent = 4 Moderate amplitude, but without mouth opening, constant or almost so = 5 Large amplitude with mouth opening, occasional = 4 Large amplitude with mouth opening, frequent = 5 Large amplitude with mouth opening, constant or almost so = 6
	Bucco-labial movements	None = 0 Borderline = 1 Clearly present, small amplitude, occasional = 3 Clearly present, small amplitude, frequent = 3 Clearly present, small amplitude, constant or almost so = 4 Moderate amplitude, forward movement of lips, occasional = 4 Moderate amplitude, forward movement of lips, frequent = 4 Moderate amplitude, forward movement of lips, constant or almost so = 5 Large amplitude, noisy smacking of lips, occasional = 5 Large amplitude, noisy smacking of lips, frequent = 5 Large amplitude, noisy smacking of lips, constant or almost so = 6
	Truncal movements	None = 0 Borderline = 1 Clearly present, small amplitude, occasional = 2 Clearly present, small amplitude, frequent = 3 Clearly present, small amplitude, constant or almost so = 4 Moderate amplitude, occasional = 3 Moderate amplitude, frequent = 4

ESRS Part	Symptom	Scoring
		Moderate amplitude, constant or almost so = 5 Greater amplitude, occasional = 4 Greater amplitude, frequent = 5 Greater amplitude, constant or almost so = 6
	Upper extremities	None = 0 Borderline = 1 Clearly present, small amplitude, movement of one limb, occasional = 2 Clearly present, small amplitude, movement of one limb, frequent = 3 Clearly present, small amplitude, movement of one limb, constant or almost so = 4 Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs, occasional = 3 Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs, frequent = 4 Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs, constant or almost so = 5 Greater amplitude, movement involving two limbs, occasional = 4 Greater amplitude, movement involving two limbs, frequent = 5 Greater amplitude, movement involving two limbs, constant or almost so = 6
	Lower extremities	None = 0 Borderline = 1 Clearly present, small amplitude, movement of one limb, occasional = 2 Clearly present, small amplitude, movement of one limb, frequent = 3 Clearly present, small amplitude, movement of one limb, constant or almost so = 4 Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs, occasional = 3 Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs, frequent = 4 Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs, constant or almost so = 5 Greater amplitude, movement involving two limbs, occasional = 4 Greater amplitude, movement involving two limbs, frequent = 5 Greater amplitude, movement involving two limbs, constant or almost so = 6
	Other involuntary movements	None = 0 Borderline = 1 Clearly present, small amplitude, occasional = 2 Clearly present, small amplitude, frequent = 3 Clearly present, small amplitude, constant or almost so = 4 Moderate amplitude, occasional = 3 Moderate amplitude, frequent = 4 Moderate amplitude, constat or almost so = 5 Greater amplitude, occasional = 4 Greater amplitude, frequent = 5 Greater amplitude, constant or almost so = 6
Part V – Part VIII		Absent = 0 Borderline = 1 Very mild = 2 Mild to moderate difficulty in initiating movements = 3 Moderate = 4 Moderately severe = 5 Marked = 6 Severe = 7 Extremely severe = 8

4.1.1.12. Laboratory values

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½*LLOQ. For values above upper limit of quantification values will be set to that limit.

4.1.1.13. Prior and concomitant medication

Prior medications are those with an end date of administration prior to the date of the first IMP administration.

Concomitant medications are those that started or continued during the study treatment period.

4.1.1.14. Pharmacokinetic parameters

PK parameters to be estimated according to the protocol:

- $AUC_{(0\text{-}24h)}$: The area under the curve of plasma concentration vs time, from time point zero up to the time 24h after administration, unit: [ng*h/mL]. $AUC_{(0\text{-}24h)}$ will be calculated according to the linear trapezoidal rule using actual sampling times and extrapolated basing on Kel if concentration at 24 h is below LLOQ.
- C_{max}: Maximum plasma concentration, unit: [ng/mL]. C_{max} defines the maximum concentration of the drug substance in plasma during dosing period. C_{max} will be obtained directly from the measured concentrations.
- $AUC_{(0\text{-}inf)}$: The area under the curve of plasma concentration vs time, from time point zero extrapolated to infinity, unit: [ng*h/mL]. $AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_t / K_{el}$, C_t is the last measurable analyte concentration in plasma and K_{el} is the terminal elimination rate constant.
- t_{max}: Time to reach maximum plasma concentration, unit: [h]. The t_{max} will be obtained directly from the actual sampling times.
- K_{el}: Terminal elimination rate constant, unit: [1/h]. K_{el} will be estimated via linear regression of time versus log of concentration. This parameter will be calculated by linear least squares regression analysis using at least last three non-zero plasma concentration values. C_{max} values will not be included in K_{el} calculation. K_{el} will only be calculated if the adjusted coefficient of determination of exponential fit (R^2 adjusted) is not less than 0.7 ($R^2 \geq 0.7$).
- $t_{1/2}$: Plasma elimination half-life, unit: [h]. The $t_{1/2}$ will be calculated as $0.693/K_{el}$.
- CL/F: apparent systemic clearance, calculated as dose administered in dosing interval divided by $AUC_{(0\text{-}inf)}$ on Day 1 or divided by $AUC_{(0\text{-}tau)}$.
- Vz/F: apparent volume of distribution; a hypothetical volume of fluid into which the drug is dispersed. It is calculated as $Dose/(K_{el}*AUC_{(0\text{-}inf)})$ for Day 1 and $Dose/(K_{el}*AUC_{(0\text{-}tau)})$ for Day 7.
- C_{trough}: the trough concentration is the concentration reached by the drug immediately before the next dose is administered as well as 24 h after the last dose administration.

4.1.2. Specifications for summary tables

For **continuous variables**, summary statistics will generally consist of sample size N, number of missing values, arithmetic mean, standard deviation (SD), median, lower and upper quantile, minimum, and maximum. Summaries of PK variables (if data transformation is necessary) will, in addition, contain the geometric mean and the coefficient of variation.

Binary/categorical variables will be summarized and displayed in frequency tables showing sample size, absolute and relative frequencies.

In general, data will be included in summary tables stratified by randomized treatment group.

4.1.3. Specifications for plots

Unless otherwise specified, plots related to continuous endpoints will take form of a bar representing LS means calculated from MMRM model and whiskers representing confidence interval. Binary endpoints will take form of a forest plot – point representing proportion of subjects meeting the endpoint and whiskers representing confidence interval.

Results from logistic regression will also take form of a forest plot – point with whiskers, where point represents odds ratio and whiskers confidence interval.

Depending on assessment of variable distribution (on basis of Q-Q plot), safety data will be presented as line and point and whisker plots (for normally distributed values) or boxplots (where there is a notable skewness of variable distribution). For line and point and whisker plots, the points will represent the mean value and whiskers – standard deviation of the mean. For boxplot top and bottom of the box will represent lower and upper quartile respectively. Thick line in the middle of the box will be median. Whiskers will represent the lowest value at most Q1-1.5*IQR (inter quantile range) and the largest value no further than Q3+1.5*IQR. Points will represent potential outliers.

Data will be shown for each randomized treatment group. Data collected during unscheduled visit will not be shown on plots unless otherwise specified.

4.1.4. Data listings

Data on listings will be listed as documented. Relevant generated and transformed variables will be listed next to the original data items. Any imputed value will be flagged.

In all listings the patient identifier and the randomized treatment group will be included. The patient identifier consists of the center and the patient number, additionally a flag specifying analysis set will be provided.

In general, patient listings will be sorted by patient identifier and visit (if applicable), unless otherwise stated.

Patient listings of data that is collected independently from visits (e.g. adverse events, medical histories or medication) will be sorted by patient identifier, day of onset or start day of administration, duration and MedDRA preferred term or base substance name, respectively.

Missing values in the listings will be represented as NA (not available) for both text and numerical data. In case of partially missing dates (when day or day and month is unknown) missing data will be represented as series of 9s – for example 2023-03 will be presented as 2022-03-99. Any imputed data will be presented separately from raw data or flagged accordingly in order to be able to review all data as collected.

4.1.5. Handling of withdrawals, missing values and outliers

For the main analyses performed using the FAS and PP population, data will be analyzed as observed during the study, no imputation rule will be applied. For continuous endpoints measured longitudinally, the missing values post baseline will be handled in a mixed model for repeated measures, where the values are assumed to be missing at random. For binary endpoints values will be used as observed – excluding any missing values from analysis.

A sensitivity analysis will be conducted for primary and secondary efficacy endpoints, whereby missing data are imputed using multiple imputation (MI) for continuous endpoints and non-responder imputation (NRI) method for binary endpoints. For multiple imputation R seed will be set as 500036.

A worst-case scenario will be used in the estimation of partial dates for adverse events and concomitant medications. That is, for an incomplete start date the first day of the month or the first month of the year will be used. For an incomplete stop date the last day of the month or the last month of the year will be used. If an estimated start date of an adverse event is earlier

than the date of day 1 or the start date is completely missing, day 1 will be used, unless documented data does not allow for this interpretation.

Whenever estimated dates will be calculated, the incomplete date will be listed and the study day will be calculated using the estimated date. These study days will be flagged as estimated in listings.

In other situations missing data will generally not be replaced or imputed unless otherwise specified in this document.

4.2. Disposition of patients

The number of patients screened, the number of patients randomized and the number of patients in each analysis population will be summarized. The reasons for exclusion from each analysis population will be summarized for all patients randomized. The reasons for non-eligibility for randomization, i.e. the violated inclusion or exclusion criteria will be listed for all non-randomized patients by visit.

Major protocol deviations (leading to the exclusion from the PP) and minor protocol deviations (not leading to the exclusion from the PP) will be summarized for the safety population. The determination of major and minor protocol deviations will be performed during the blind data review meeting documented in the blind data review meeting minutes, which will be finalized prior to unblinding of the treatment group for the main analysis of data of the double-blind treatment. In addition a listing of subjects excluded from PP population and pharmacokinetic populations will be provided with specification of reason for exclusion for analysis.

The number of patients who completed the study and the number of patients who terminated the study early will be summarized in frequency tables for the safety, the FAS and the PP populations.

The timing of early termination will be summarized for each study month for the safety, the FAS and the PP populations.

Consolidated Standards of Reporting Trials (CONSORT) diagram (Moher et al. 2001) will be used to present abovementioned data in a graphical form.

4.3. Demographics and baseline characteristics

Demographic data and other baseline characteristics will be summarized for Safety, FAS, PP and PSPC population by treatment group and overall. The following variables will be summarized:

- Age (years) as continuous variable [(date of ICF signature – date of birth)/365.25]
- Race/ethnicity (White vs Other).
- Sex (male / female)
- Body weight without shoes [kg] and height without shoes [cm] at screening and baseline
- BMI [kg/m^2] calculated as Weight (kg)/[height (m^2)] at screening and baseline.

Weight, height and BMI will be shown both for screening and baseline (Day -1) visit.

Disease characteristic will summarize:

- Duration of disease [years]
- Duration of current exacerbation [days]

- Screening and baseline PANSS score as continuous variable (positive subscale, negative subscale, general psychopathology subscale, total score, Marder 5-factor model subscales)
- Screening and baseline PANSS score as category (low <95, high ≥95)
- Screening and baseline CGI-S items as numerical variable
- Baseline BACS T-score as continuous variable for each task and a composite value.

Separate table will present descriptive statistics for ESRS subscales.
A table will present descriptive statistics for vital signs measured during Screening and Baseline (Day -1) visit: blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute], body temperature [°C]. Blood pressure and heart rate will be presented for three time points:

- after 3 minutes lying down
- after 3 minutes sitting, immediately upon standing
- after 3 minutes standing.

Physical examination table will combine results from screening and baseline – in case of new abnormalities observed on Day 1, worst case will be presented in table.

The 12-lead ECG results will be summarized for following parameters: heart rate, ECG finding, PR Value, QRS Value, RR Value, QT Value, QTcF Value

Other baseline characteristics will be listed only.

All other screening or day 1 safety assessments will be listed only unless specified differently below.

4.4. Medical history

Current medical conditions are defined as those entries in medical history that are ongoing at the screening visit. Medical histories and current medical conditions will be coded using a MedDRA dictionary (version of MedDRA current at the time of database lock will be used). Medical histories and current medical conditions will be summarized by treatment group and overall for the full analysis set.

4.5. Concomitant medication

Prior and concomitant medications will be classified using the ATC codes contained in Register of Medicinal Products Approved for Marketing on the territory of the Republic of Poland[1]. Summary of concomitant medications will be provided as count and frequency for ATC level 2 (therapeutic subgroup) and 4 (chemical subgroup). Listings of prior and concomitant medications will be provided and sorted by site, patient number, name of active substance, and date of last administration (if known).

4.6. Pharmacokinetic endpoints

The concentration of CPL500036 in plasma will be summarized by dose at each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Plasma PK parameters for CPL500036 will be summarized by dose for subjects with extensive and sparse PK separately using descriptive statistics.

[1] https://rejestrymedyczne.ezdrowie.gov.pl/rpl/search/public

The concentration-time data will be summarized descriptively in tabular and graphical formats (linear and log scales). The PK parameter data will be listed and summarized descriptively in tabular format.

Analyses will be performed for PS and PSPC populations.
The following pharmacokinetic parameters will be estimated if data permits: C_{max}, $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}24h)}$, t_{max}, CL/F, Vz/F, C_{trough}, K_{el} and $t_{1/2}$ for CPL500036. They will be computed using non-compartmental modelling approach using actual sampling times. If multiple peaks occur, the highest post-dose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported. The pharmacokinetic parameters will be derived individually for each subject (and day of study if applicable).
All individual pharmacokinetic parameters i.e.: will be presented in listings and analyzed with descriptive summary statistics including arithmetic mean, geometric mean, median, standard deviation (SD), coefficient of variation (CV), minimum and maximum.
Plasma concentration/time curves will be presented in linear and semi-logarithmic scale. Curves will be presented separately for extensive and sparse sampling for:

- individual subjects (including additional semi-logarithmic scale plot showing points used for Kel calculation),
- means for all CPL500036 doses separately for Days 1 and 7,
- means for all days (Days 1 and 7) of study separately for each CPL500036 dose,
- overlapping individual curves (with mean curve in different color) for each CPL500036 dose and for each day of study (Days 1 and 7).

For the individual subject concentration-time graphs, the drug concentrations should be plotted against time using the actual sampling times. For the mean concentration-time graphs the drug concentrations should be plotted using the nominal sampling times.

Additional plasma concentration/time box plots with individual points will be presented for extensive sampling (Days 1 to 7 and Day 28) and sparse sampling (Days 1, 7, and 28) for:

- pre-dose,
- 2 h after administration.

Missing drug concentration data (no value) will be omitted from PK calculations. Drug concentration data below LLOQ will be treated in pharmacokinetic analysis as follows:
1. If the concentration below LLOQ is recorded after the last measurable concentration in the dosing interval, then it is omitted from calculations.
2. In other cases the concentration below LLOQ concentration value is set to zero.
3. If an entire concentration-time profile below LLOQ, the profile will be excluded from the PK analysis.
4. A profile of patient with very low concentrations will be excluded from the PK analysis. A profile is considered to have very low concentrations if the $AUC_{(0\text{-}24h)}$ for that day is less than 5% of the geometric mean $AUC_{(0\text{-}24h)}$, which should be calculated without inclusion of data from the patient.

4.7. Efficacy endpoints

4.7.1. Primary efficacy endpoint

The main analysis will be based on FAS population with supportive analyses using PP population data and imputed FAS population as sensitivity analysis.

For the primary efficacy analysis, change from baseline in the PANSS positive subscale score to week 4 of treatment phase will be analyzed using a mixed model for repeated measures (MRMM), with treatment (placebo, 20 mg, 40 mg), timepoint (all measurements throughout the study will be taken into account: day 1, week 1, week 2, week 3, week 4) and clinical site as fixed effects and baseline score as a continuous covariate. If there will be many clinical sites with few subjects, they can be pooled into bigger groups so the minimum of subjects per grouping will be at least five. Subject will be treated as a random effect, with an unstructured covariance structure to account for the correlation among repeated measurements. If the model does not converge, another covariance structure, (e.g., AR(1), CS, etc.) will be explored. Missing data will be assumed to be missing at random. The R formula which will be used for such analysis:

*mmrm(CHANGE ~ TREATMENT * TIMEPOINT + SITE + BASELINE + us(VISIT|ID)*

using *mmrm()* function from mmrm library.

Pearson residuals will be used to identifying outlying observations and the appropriateness of the covariance structure. Normalized or scaled residuals will be used to check for normality and will be assessed graphically. Residuals from the primary model will be plotted against the predicted values and a quantile-quantile (QQ)-plot of the residuals versus the expected quantiles of the standard normal distribution will be presented.

The statistical model will allow for comparison of efficacy between placebo and 20 mg, 40 mg, of CPL500036 at each of the timepoint. In order to compare each concentration of CPL500036 to placebo, LS means, their 90% CI, and p values will be calculated using emmeans (Estimated Marginal Means, aka Least-Squares Means) function of emmeans library.

As the null hypothesis is that there are no differences in the primary endpoint between either dose group compared to placebo at week 4, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 10% significance level, no adjustment for multiplicity will be performed for comparisons of each concentration of CPL500036 to placebo at week 4.

Moreover, change from baseline in PANSS positive subscale score at week 1, 2 and 3 will be analyzed on basis of LS-means calculated by MRMM model used in primary endpoint analysis without adjustment for multiplicity.

A sensitivity analysis will be conducted for FAS population whereby missing data is imputed using multiple imputation. Based on that approach, rather than replacing missing values with a single value, we use the distribution of the observed data/variables to estimate multiple possible values for the data points. This allows us to account for the uncertainty around the true value and obtain approximately unbiased estimates. Multiple imputation will be performed using *rbmi* library using a pre-specified seed for random number generator (see section 4.1.5).

The statistical model will allow for comparison of efficacy between placebo and 20 mg, 40 mg of CPL500036.

Descriptive statistics for change from baseline in PANSS positive subscale score at week 4 will be presented by site and by rater as a part of sensitivity analysis.

4.7.2. Secondary efficacy endpoint

All secondary endpoints will be analyzed without adjustment for multiplicity. The secondary endpoints, which are continuous:

- Change from baseline in PANSS positive subscale at Week 1, 2 and 3 [Time Frame: Weeks 1, 2, and 3].
- Change from baseline in PANSS Total Score at Weeks 1, 2, 3, 4 [Time Frame: Weeks 1, 2, 3, and 4].
- Change from Baseline in PANSS Subscales Using the Marder 5-factor Model at Weeks 1, 2, 3, and 4 [Time Frame: Weeks 1, 2, 3, and 4].
- Change from Baseline in PANSS Negative Subscales at Weeks 1, 2, 3 and 4 [Time Frame: Weeks 1, 2, 3, 4].
- Change from Baseline in PANSS general psychopathology Subscale at Weeks 1, 2, 3 and 4 [Time Frame: Weeks 1, 2, 3, 4].
- Change from Baseline in Clinical Global Impression - Severity (CGI-S) Score at Weeks 1, 2, 3, and 4 [Time Frame: Weeks 1, 2, 3, 4].
- Change from Baseline in Brief Assessment of Cognition in Schizophrenia (BACS) Score at Weeks 2 and 4 [Time Frame: Weeks 2 and 4].

will be analyzed using the same approach as described for the primary endpoint using MMRM. Change from baseline in PANSS positive subscale at Week 1, 2 and 3 will be analyzed using primary endpoint MMRM model coefficients to calculate LS means for placebo vs treatment arms comparisons.

Missing data will be assumed to be missing at random. At each timepoint, the LS-means will be reported (by treatment group and for the treatment difference for each dose group, compared to placebo).

The secondary endpoints which are binary (i.e., responder/non-responder):

- Percentage of Clinical Responders Based on the PANSS Total Score. A clinical responder is defined as a ≥ 30% decrease from baseline, [Time Frame: Weeks 1, 2, 3, 4].
- Clinical Global Impression Scale - Improvement (CGI-I) Score at Weeks 1, 2, 3, 4 [Time Frame: Weeks 1, 2, 3, 4].
- Percentage of Responders Based on CGI-I Ratings Score at weeks 1, 2, 3, 4. A responder is defined as a rating of ‘much improved’ or ‘very much improved’. [Time Frame: Weeks 1, 2, 3, 4].

will be analyzed at each timepoint using proportion of subjects who meets the criteria together with confidence intervals, difference from placebo with confidence interval and p value for comparison vs. placebo calculated using a 2-sided 10% significance level proportion test. Logistic regression model will be prepared to explain achievement of response at any time with following factors: treatment (placebo will be the reference value), baseline PANSS Total Score and site as a covariate. If there will be many clinical sites with few subjects, they can be pooled into bigger groups or countries.

In sensitivity analysis for continuous endpoints, similarly to primary endpoint multiple imputation will be used. Binary endpoints analysis will be performed based on non-responder imputation.

4.7.3. Subgroup analyses for efficacy endpoints

Analyses described in 4.7.1 and 4.7.2 will be performed in subgroups defined in 3.2 (with sex dropped from model specification when analyzing males and females independently).

4.8. Safety analyses

Safety data will be summarized for the safety population (SS).

4.8.1. Adverse event analysis

Any undesirable signs, symptoms or medical conditions occurring or worsening of pre-existing conditions between signing informed consent and the first administration of the study medication are considered as pre-treatment AEs. Undesirable signs, symptoms or medical conditions or worsening of pre-existing conditions occurring after the first administration of study medication are considered as treatment emergent adverse events (TEAEs).

A TEAE will be analyzed as related to study medication (i.e. as adverse drug reaction, ADR) if the relationship to study treatment was documented as ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’ or if the relationship to study treatment is missing.

An overview table presenting the incidence of the following AE categories will be presented. Percentage of patients in each category will be compared between treatments as a difference in proportions between treatments including a 95% CI based on the Agresti – Caffo method (2000):

- All AEs
- Pre-treatment AEs
- Serious AEs (SAEs) (including pre-treatment SAEs)
- Treatment emergent AEs (TEAEs)
- Treatment emergent SAEs (TESAEs)
- Severe TEAEs
- Related TEAEs
- Related severe TEAEs
- TEAEs leading to reduction of dose
- TEAEs leading to interruption of dose
- TEAEs leading to permanent discontinuation (i.e. withdrawal) of study medication
- Related TEAEs leading to permanent discontinuation of study medication
- AEs leading to death (i.e. outcome of AE is fatal)
- TEAEs leading to death
- Related TEAEs leading to death

All treatment emergent AEs (TEAEs) and all serious TEAEs will be tabulated by MedDRA SOC and PT presenting the number and percentage of patients reporting the AE and the number of AEs reported. Additional tables will distinguish the events by whether the AE was related to study medication and by maximum severity.

All AEs documented in the eCRF will be listed by patient. Data listings will include patient ID, treatment group, verbatim term, preferred term, system organ class, start and stop date and relative day of the AE, severity, medications (yes/no), seriousness, action taken with study medication, relationship to study medication, and outcome will be provided. TEAEs will be flagged as such. In addition, separate listings for all SAE’s, deaths and AEs leading to discontinuation (action taken with study treatment = drug withdrawn, or AE is reason for early termination) will be presented.

4.8.2. Safety laboratory data

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listings.

Laboratory data will be summarized by type of laboratory test after all results are converted to standard SI units (according to algorithms presented in Data Validation Plan). Descriptive statistics will be calculated for each laboratory parameter at baseline (Day 1) and at each scheduled time point. Shift tables using the categories 'lower than normal range', 'within normal range' and 'higher than normal range' will be provided for each numeric parameter, comparing the baseline value to all post-baseline values. For results expressed as category (in urinalysis) shift tables will present categories: normal and abnormal. Moreover, change from baseline values will also be presented.

Other urinalysis parameters, than those pre-specified in the eCRF, will be listed only.

4.8.3. Other safety data

4.8.3.1. Vital signs

These summaries will take form of tables for raw data and changes from baseline (Day 1) as well as percentage of abnormal values.

Shift tables using the categories 'lower than normal range', 'within normal range' and 'higher than normal range' will be provided for each parameter (where applicable), comparing the baseline value to all post-baseline values. Categorization of blood pressure is performed for both SBP and DBP at once, so one shift table will be prepared only for blood pressure.

Change from baseline values in vital signs will take form of boxplots (and/or point and whisker plots) for each study arms for each vital sign parameter.

Listings flagging abnormal values will be also produced.

4.8.3.2. Electrocardiograms

ECG variables that will be analyzed include heart rate, ECG finding, PR, QRS, RR, QT and QTcF value.

ECG summaries will take form of tables for raw data and changes from baseline (values collected during Day -1 visit) as well as percentage of abnormal values. In addition, shift tables presenting number of patients that either developed abnormalities in PR, QRS, RR, QT and QTcF value (or had such abnormalities subsume) since baseline will be provided.

The number of patients with at least one clinically relevant finding detected during the ECG examination will be summarized in frequency tables for each scheduled assessment or visit.

Change from baseline values of ECG parameters will take form of boxplots for each study arms.

4.8.3.3. Physical examination

Abnormal findings occurring after screening and baseline visit (after Day 1) will be listed. No summaries beside baseline are planned.

4.8.3.4. Neurological, ophthalmological, dermatological

examination

Results of such examination will be listed only. No summaries are planned.

4.8.3.5. Extrapyramidal Symptom Rating Scale (ESRS)

ESRS was developed to assess four types of drug-induced movement disorders (DIMD): Parkinsonism, akathisia, dystonia, and tardive dyskinesia. It will be performed once at Screening (Day -10 to -2); once at Baseline (Day -1), once on Day 1, 7, 14, 21 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (it will be performed after PANSS, CGI-S, CGI-I and BACS); once during the follow-up visits. A baseline assessment will be performed at Day -1 and repeated on days 7, 14, 21, 28 and follow-up visits. Descriptive statistics of the score and changes from baseline will be presented by treatment and overall in both tabular and graphical form. In case of the latter, boxplots will be used.

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

The Columbia-Suicide Severity Rating Scale is used to evaluate suicidal ideation and behavior. Some data collected on the C-SSRS are not used for analysis but are used for individual clinical management and safety monitoring (e.g., suicidal behavior lethality and suicidal ideation intensity). These data are not included in the proposed analysis tables.
The following outcomes are C-SSRS categories and have binary responses (yes/no). Using the C-SSRS, potentially suicide-related events will be summarized using the following categories:

- 1 – Wish to be Dead
- 2 – Non-specific Active Suicidal Thoughts
- 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- 5 – Active Suicidal Ideation with Specific Plan and Intent
- 6 – Preparatory Acts or Behavior
- 7 – Aborted Attempt
- 8 – Interrupted Attempt
- 9 – Actual Attempt (non-fatal)
- 10 – Completed Suicide

In addition following endpoints will be determined: Suicidal Ideation (any positive responses in categories 1 to 5), Suicidal behavior (any positive responses in categories 6-10) and Suicidal Ideation or Behavior (any positive responses in categories 1-10).
A frequency distribution at each scheduled time point by arm will be provided. Shifts from baseline values for past 6 months will be summarized by treatment.
If less than five subjects have positive answers in 1 to 10 categories then only a listing will be prepared.

4.8.4. Exposure and drug adherence

Exposure and extent of exposure as well as data on drug adherence will be presented in tabular form with descriptive statistics.

4.9. Exploratory endpoints

Not applicable.

4.10. Additional analyses

An exploratory PK analysis, not described in the protocol, will be performed if data permits for CPL500036:

- %extrapolated AUC
- $AUC_{(0\text{-}tau)}$: The area under plasma concentration-time in the dosing interval, i.e. from time zero to exactly 24 hours, unit: [ng*h/mL]. $AUC_{(0\text{-}tau)}$ will be calculated according to the linear trapezoidal rule using actual sampling times and (if necessary) extrapolated or interpolated to exactly 24 h.
- accumulation calculated as $AUC_{(0\text{-}24h)}$ ratio Day 7/Day 1
- accumulation ratio for C_{max} ratio Day 7/Day 1
- evaluation of steady-state
- linearity of dose-normalized C_{max} and $AUC_{(0\text{-}24h)}$
- evaluation of changes in T_{max} (median and range) between doses and days of study
- evaluation of changes in $T_{1/2}$ (mean ± SD) between doses and days of study
- evaluation of changes in CL/F (mean ± SD) between doses and days of study
- evaluation of changes in Vz/F (mean ± SD) between doses and days of study
- evaluation of intra-subject variability in AUC between $AUC_{(0\text{-}inf)}$ for Day 1 and $AUC_{(0\text{-}tau)}$ for Day 7
- fluctuation on Day 7
- swing on Day 7

Additional PK parameters may be determined where appropriate.
An exploratory PK/PD analysis of pharmacokinetic parameters of CPL500036 as well as PD assessments may be performed if deemed appropriate following review of the summary PK and PD data. The decision to perform this analysis will be made by the Sponsor upon review of the tables, figures and listings produced at the end of the study.
Details of these analyses (as well as results) will be presented in a document separate from the clinical study report.

5. Software and statistical programming

R programming will be performed according to [redacted] SOP “Data analysis” and related work instructions. The statistical analysis will be performed using the R statistical software package (Version 4.0.3 or later).

PK parameters will be calculated by Celon Pharma using Phoenix WinNonlin 8.4 or later, except C_{trough}, accumulation ratio for $AUC_{(0\text{-}24h)}$, and accumulation ratio for C_{max}.

PK parameters C_{trough}, accumulation ratio for $AUC_{(0\text{-}24h)}$, and accumulation ratio for C_{max} calculations and all other than PK parameters analyzes will be performed by CleanDataLabs using R 4.1.3 or later version software, based on the results obtained from the PK parameters calculations performed using WinNonlin or raw data on analyte concentrations.

6. Reference

ICH Topic E9: Statistical Principles for Clinical Trials, 5 February 1998, adopted by CPMP, March 1998, issued as CPMP/ICH/363/96; adopted by FDA in September 1998

ICH Topic E10: Choice of Control Group and Related Issues in Clinical Trials, adopted by CPMP, 20 July 2000, issued as CPMP/ICH/364/96; adopted by FDA in May 2021

ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms, adopted by CHMP on 25 July 2024, issued as EMA/CHMP/ICH/953493/2022; adopted by FDA in October 2024

R Development Core Team. 2023. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. http://www.R-project.org.

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