Clinical Study Protocol

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

Sponsor:	Celon Pharma S.A. Ogrodowa 2A Str. 05-092 Łomianki/ Kiełpin Poland
Sponsor Study Number:	02PDE2019
EudraCT Number:	2020-002316-51
IMP Name:	CPL500036
Development Phase:	Phase II
Version (Date) of Final Protocol:	version 4.0 (16 May 2024)

This clinical study will be conducted in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) E6(R2), the protocol and with other applicable regulatory requirements.

Confidentiality Statement

SIGNATURE PAGE

Declaration of Sponsor

I have read and understood the protocol version 4.0, dated 16th May 2024, specified below, and agree on the contents.

Protocol Title: 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.

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory

SIGNATURE PAGE

Declaration of the Investigator

I have read and understood the protocol version 4.0, dated 16th May 2024, specified below, and agree on the contents1

Protocol Title: 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.

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice applicable to this clinical study.

I have read all pages of this clinical study protocol, version 4.0, dated 16th May 2024 and confirm that it contains all the information required to conduct this study. I agree to conduct the study as detailed in the protocol and comply with all the terms and conditions set out therein. I confirm that I is to conduct the study in accordance with the provisions of the Declaration of Helsinki. I will also ensure that Investigator(s) and other relevant members of my staff have access to copies of this protocol and the Declaration of Helsinki to enable them to work in accordance with the provisions of the documents and standard operating procedures of designated CRO company. Furthermore, current ICH-GCP, and local regulations is to be followed.

I acknowledge that all data included in the clinical study protocol are confidential. Copying, disclosing and publishing without assent of Sponsor is prohibited.

Investigator Signatory

SIGNATURE PAGE

Declaration of Statistician

I have read and understood the protocol version 4.0, dated 16th May 2024, specified below, and agree on the contents.

Protocol Title: 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.

Statistician Signatory

LIST OF STUDY STAFF/ RESPONSIBLE PARTIES

Sponsor Sponsor's representative	[redacted]
Sponsor Project Management	
Study Coordinator	
CRO Project Management	
Serious Adverse Event Reporting	

Medical Monitor	[redacted]
Bioanalytical Laboratory	
Biostatistics	
Funding	

AMENDMENT 7 – Protocol v. 3.3 dated 22 November 2023→ Protocol v. 4.0 dated 16 May 2024	
Applicable Section	**Description of Change(s)**
Rationale: The introductions of amendments in statistical parts without any substantial amendments	
1.1. Protocol Synopsis, Statistical Methods	The following text has been changed: **Data Presentation/Descriptive Statistics:** *Analysis Sets:* • 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 Set (SS): All patients who received at least 1 dose of study treatment (either CPL500036 or placebo). • Pharmacokinetic Set (PS): All subjects in the safety set with at least 1 **evaluable** PK parameter. ~~**evaluable and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of CPL500036.**~~ • Pharmacokinetic Set for parameter calculation (PSPC): All subjects 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 ~~**select**~~ 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. […] *Primary Efficacy Analysis:* The null hypothesis is that there is no difference in the primary endpoint between either dose group compared to placebo, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 10% significance level. The primary endpoint will be analysed using a mixed effect repeated measures model (MRMM), with treatment, ~~**and**~~ time point, **clinical site and interaction between clinical site and timepoint** as fixed effects and baseline score as a covariate. **If there will be many clinical sites with few subjects, they can be pooled into bigger groups**. 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. A sensitivity analysis will be conducted whereby missing data is imputed using multiple imputation. The primary analysis will compare each dose group with placebo, **based on estimated marginal means (aka least square means, LS-means) from the model** without adjustment for multiplicity. As a secondary analysis of the primary endpoint a comparison of both treatment groups pooled, compared to placebo will also be made. *Secondary Efficacy Analyses:* All secondary endpoints will be analysed without adjustment for multiplicity. The secondary endpoints, which are continuous, will be analysed using the same approach as described for the primary endpoint. Missing data will be assumed to be missing at random. At each time point, 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) will be analysed at each time point using a Logistic regression model with treatment **and clinical site (or country if there will be many clinical sites)** as a fixed effect and baseline score as a covariate. If a patient is missing data in order to derive their response at a given time point, the missing data will be imputed using multiple imputation **for continuous endpoints and non-responser imputation for binary endpoints** prior to the analysis.
10.1.3. Analysis population	The following text has been changed: • 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 Set (SS): All patients who received at least 1 dose of study treatment (either CPL500036 or placebo). • Pharmacokinetic Set (PS): All subjects in the safety set with at least 1 **evaluable** PK parameter. ~~**evaluable and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of CPL500036.**~~ • Pharmacokinetic Set for parameter calculation (PSPC): All subjects 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 ~~**select**~~ 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.

	[…]
10.3. Primary Efficacy Analysis	The following text has been changed: The null hypothesis is that there is no difference in the primary endpoint between either dose group compared to placebo, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 10% significance level. The primary endpoint will be analysed using a mixed effect repeated measures model (MRMM), with treatment, ~~**and**~~ time point, **clinical site and interaction between clinical site and timepoint** as fixed effects and baseline score as a covariate. **If there will be many clinical sites with few subjects, they can be pooled into bigger groups**. 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. A sensitivity analysis will be conducted whereby missing data is imputed using multiple imputation. The primary analysis will compare each dose group with placebo, **based on estimated marginal means (aka least square means, LS-means) from the model**.
10.4. Secondary Efficacy Analysis	The following text has been changed: *Secondary Efficacy Analyses:* All secondary endpoints will be analysed without adjustment for multiplicity. The secondary endpoints, which are continuous, will be analysed using the same approach as described for the primary endpoint. Missing data will be assumed to be missing at random. At each time point, 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) will be analysed at each time point using a Logistic regression model with treatment **and clinical site (or country if there will be many clinical sites)** as a fixed effect and baseline score as a covariate. **In sensitivity analysis,** if a patient is missing data in order to derive their response at a given time point, the missing data will be imputed using multiple imputation **for continuous endpoints and non-responder imputation for binary endpoints** prior to the analysis.
10.8. Demographic and Anthropometric Information and Baseline Characteristics	The following text has been changed: Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight and BMI) will be listed by subject. Demographic characteristics (age, sex, ethnicity and race) and anthropometric characteristics (height, weight and BMI) will be summarized by treatment and for all subjects in the ~~**safety analysis set**~~ **FAS, SS, PP and PSPC populations.** The denominator for percentages will be

	the number of subjects in the ~~**safety analysis set**~~ **given analysis set** for each treatment or for all subjects as applicable. Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA SOC, MedDRA preferred term, start date, and stop date (or ongoing if applicable), **as well as summarized by treatment group and overall for full analysis set**
10.9. Prior and Concomitant Medication and Drug Administration	The following text has been changed: Prior medications are those that started and stopped prior to the first dose of IMP. Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after). Prior and concomitant medication will be **classified using the ATC codes contained in Register of Medicinal Products Approved for Marketing on the territory of the Republic of Poland and** listed by subject and will include the following information: reported name, preferred term, **ATC level 2 (therapeutic subgroup) and 4 (chemical subgroup)**, the route of administration, dose, frequency, start date/time, duration and indication. **Summary of prior and concomitant medications will be provided as a count and frequency for ATC level 2 and 4.** ~~**Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) latest version.**~~ Drug administration dates and times will be listed for each subject.
10.11.1. Adverse Events	The following text has been changed: All AEs will be listed. The number and percent of subjects experiencing an event will be tabulated for each SOC and preferred term. The AEs will also be tabulated according to intensity and causality. **An overview table presenting the incidence of AE will be presented. All tables will be prepared separately by number of patients and number of events.** Serious AE will be listed separately**.**
10.11.2. Clinical Laboratory Test	The following text has been changed: 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.

	Clinical laboratory tests (observed values) **as well as change from baseline and categorization of results** will be summarized descriptively in tabular format. Shift tables will be presented for select**ed** laboratory parameters.
10.11.3. Vital Signs	The following text has been changed: Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital signs findings that were considered AEs by the Investigator will be presented in the AE listings. Observed values as well as change from baseline ~~**data**~~ will be summarized descriptively in tabular
10.11.4. Standard 12-lead Electrocardiogram	The following text has been changed: Standard 12-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values will be summarized descriptively in tabular format. Change from baseline will be summarized descriptively for ~~**QTc data**~~ all parameters. A categorical ~~**QTc**~~ analysis will also be performed **as well as shift tables.**
10.15. Timing of analysis	The following point has been added: **Baseline characteristics 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.**
The points numeration was updated.	

SUMMARY LIST OF CHANGES

AMENDMENT 6 – Protocol v. 3.2 dated 01 September 2022→ Protocol v. 3.3 dated 22 November 2023	
Applicable Section	**Description of Change(s)**
List of study stuff / responsible parties	The Medical Monitor has been changed.

AMENDMENT 5 – Protocol v. 3.1 dated 14 July 2021→ Protocol v. 3.2 dated 01 September 2022	
Applicable Section	**Description of Change(s)**
List of study stuff / responsible parties	Due to the change of the CRO company, the corresponding data has been updated. Additionally, the Statistical Part Consultant and Medical Monitor have been changed.

AMENDMENT 4 – Protocol v. 3.0 dated 03 March 2021 → Protocol v. 3.1 dated 14 July 2021	
Applicable Section	**Description of Change(s)**
Rationale: Addition of Day 0 to the Study Schedule	
1.1. Protocol synopsis, Study design	The following text has been modified: "(…) 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**~~ **randomization on Day 0**. The duration of the Medication Washout Period may be shorter or omitted for non-medicated patients."
1.1. Protocol synopsis, Study Population,	The following text has been added: "**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening and on Day -1. If a patient status after screening changes at baseline (Day -1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). **It should be remembered that all baseline procedures must be performed on Day -1, but final patient qualification should be made when all results are available, before randomization on Day 0."**
1.2. Schema, Study Overview	The Figure 1 was updated.
1.3. Schedule of Assessments, Time Points and Window Allowance	The Table 1 was updated.
1.3. Schedule of Assessments, Footnotes for Table 1	The following text has been modified: "b) Patients that fulfil all the inclusion criteria and none of the exclusion criteria will then be admitted to the Clinical Unit on Day -7 and enter a Medication Wash-out Period of up to 7 days **(Day -7 to Day -1)** before the **randomization on Day 0.** ~~**start of the Treatment Period (Day -7 to Day -1).**~~ The duration of the Medication Washout Period may be shorter or omitted for non-medicated patients."
4.1 Overview	The following text has been modified: "(…) 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**~~ **randomization on Day 0**. The duration of the Medication Washout Period may be shorter or omitted for non-medicated patients."
5. Study population	The following text has been added: "**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening and on Day -1. If a patient status after

	screening changes at baseline (Day -1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). **It should be remembered that all baseline procedures must be performed on Day -1, but final patient qualification should be made when all results are available, before randomization on Day 0."**
6.4.2. Randomization Numbers	The following text has been modified: "Prior to dosing, on Day **0** ~~**-1**~~, subjects will be assigned a randomization number in accordance with the randomization code generated by eCRF platform. (…)"
8.7. Hospitalization	The following text has been modified: "Patients are to be hospitalized after the screening qualification for washout period of up to 7 days (if necessary) before the ~~**start of the 28-day Treatment Period**~~ **randomization on Day 0**. Patients are to be hospitalized during the treatment period (Day 1 to Day 28). On Day 29 patients may be discharged from the clinical centre based on local standards of care if the patient is in stable condition under the regular medication(s)."
9.2. Baseline (Day -1)	The following text has been modified: "After all the procedures Investigator is to confirm that the inclusion/ exclusion are met. If a patient status after screening changes at Baseline (Day -1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). **It should be remembered that all baseline procedures must be performed on Day -1, but final patient qualification should be made when all results are available, before randomization on Day 0.** ~~**For a patient meeting all of the inclusion and none of the exclusion criteria the randomization procedure is to be performed.**~~**"**
9.3. Day 0	The following text has been added: **"On Day 0, the Investigator is to performed the final patient qualification to the study based on all baseline results – this is the case, when not all baseline results (especially laboratory values) are to be available on Day -1.** **For a patient meeting all of the inclusion and none of the exclusion criteria the randomization procedure is to be performed."**
Rationale: Shortening the duration of Screening Period	

1.1. Protocol synopsis, Study design	The following text has been modified: **"**For the Screening Period, patients will undergo screening assessments from Day ~~-11~~ **-10** to Day -8 in multiple settings (i.e., emergency departments, outpatient clinics, etc.) (…)"
1.2. Schema, Study Overview	The Figure 1 was updated.
1.3. Schedule of Assessments, Time Points and Window Allowance	The Table 1 was updated.
1.3. Schedule of Assessments, Footnotes for Table 1	The following text has been modified: "a) Patients will undergo screening procedures over up to **4 3** days on an in-house basis in multiple settings (i.e., emergency departments, outpatient clinics, etc.). d) Extrapyramidal side effects will be monitored, using the ESRS. It will be performed once at Screening (Day ~~-11~~ **-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. e) C-SSRS will be conducted once at Screening (Day ~~-11~~ **-10** to -2); once at Baseline (Day -1); on Day 14 and Day 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, BACS and ESRS); once during the follow-up visits (after ESRS). f) Respiratory rate, body temperature, 3-positional blood pressure and pulse (after 3 minutes lying down; after 3 minutes sitting, immediately upon standing; and after 3 minutes standing) will be taken once at Screening (Day ~~-11~~ **-10** to -2); once at Baseline (Day -1); thrice on Day 1, Days 2-6, Day 7, 14, 21 and 28 predose (≤ 1h before 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 ~~-11~~ **-10** to -2); once at Baseline (Day -1); on Day 7, 14, 21 and 28 pre-dose (≤ 1h before IMP administration); once during the follow-up visits."
4.1. Overview	The following text has been modified: "For the Screening Period, patients will undergo screening assessments from Day ~~-11~~ **-10** to Day -8 in multiple settings (i.e., emergency departments, outpatient clinics, etc.) (…)"

4.5. Study Duration	The following text has been modified: "The duration of participation for each subject will be approximately 8 weeks. The estimated study duration includes: 1. Screening Period: Up to ~~**11**~~ **10** days. 2. Treatment Period: Days 1 to 28. 3. Follow-up Period: 7 to 14 days after the post-last dose of IMP (Day 28) – Days 35 to 42."
8.3.4. Vital Signs	The following text has been modified: "Respiratory rate (breaths per minute), body temperature (°C), 3-positional blood pressure (systolic and diastolic [mmHg]) and pulse (beats per minute [bpm]) (after 3 minutes lying down; after 3 minute sitting, immediately upon standing; and after 3 minutes standing) will be taken taken once at Screening (Day ~~**-11**~~ **-10** to -2); once at Baseline (Day -1); thrice on Day 1, Days 2-6 (each day), Day 7, 14, 21 and 28: pre-dose (≤ 1h before IMP administration) and within 5 minutes before or after 1h 45 minutes and 9h post-dose; once during the follow-up visits."
8.3.5. Standard 12-lead Electrocardiograms	The following text has been modified: "(…) The ECGs will be performed once, pre-dose (≤ 1h before IMP administration) at all scheduled visits when IMP is administered. • Once at Screening (Days ~~**-11**~~ **-10** to -2) and at Baseline (Day -1), • On Days 7, 14, 21 and 28: pre-dose, • On Follow-up Visits (Days 35 to 42)."
8.3.6. Physical Examination	The following text has been modified: Physical examinations will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below: • at Screening (Days ~~**-11**~~ **-10** to -2) and at Baseline (Day -1), • On Day 28; not earlier than 5h post-dose, • On Follow-up Visits (Days 35 to 42)."
8.3.9 Additional Safety Variables	The following text has been modified: "Neurological, ophthalmological, and dermatological examinations will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below: Neurological examinations: • At Screening (Days ~~**-11**~~ **-10** to -2) and at Baseline (Day -1), • On Days 7, 14, 21 and 28; not earlier than 5h post-dose,

	• On Follow-up Visits (Days 35 to 42). Ophthalmological examinations: • At Screening (Days ~~-11~~ **-10** to -2) and at Baseline (Day -1), • On Day 28 not earlier than 5h post-dose. Dermatological examinations: • At Screening (Days ~~-11~~ **-10** to -2) and at Baseline (Day -1), • On Day 28; not earlier than 5h post-dose.”
8.5.1. Positive and Negative Syndrome Scale	The following text has been modified: “The efficacy assessment (PANSS) will be performed once at Screening (Day ~~-11~~ **-10** to -2); once at Baseline (Day -1); on Days 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 before any other scale).”
8.5.2. Clinical Global Impression Scale - Severity	The following text has been modified: “The efficacy assessment (CGI-S) will be performed once at Screening (Days ~~-11~~ **-10** to 2), once at baseline (Day -1); on Days 7, 14, 21 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (after PANSS). “
9.1. Screening	The following text has been modified: “Patients will undergo screening assessments from Day ~~-11~~ **-10** to Day – 8 in multiple settings (i.e. emergency departments, outpatient clinics etc.) (…)”
Rationale: Addition of clarification note regarding Concomitant Treatment	
5.4.3. Prior and Concomitant Treatments	The following text has been added: **“Precaution should be exercised in patients using concomitant treatment with agents being BCRP (Breast Cancer Resistance Protein) substrates (e.g. ezetimibe, pravastatin, rosuvastatin), as the Investigational Product may inhibit the BCRP. As per Table 9, the dose of these drugs should be stable within 1 month prior to Screening to allow objective patient’s follow up. Any confusions related to the changes in patient’s status and/or laboratory results should be discussed with the Medical Monitor.”**

AMENDMENT 3 – Protocol v. 2.1 dated 21 December 2020→ Protocol v. 3.0 dated 03 March 2021	
Applicable Section	**Description of Change(s)**
Rationale: Extension of explanation without any substantial amendments (in accordance with the Hungarian Regulatory Authority recommendation).	
2.5. Risk-benefit Assessments	The following text has been added: **"Current antipsychotics used in patients with schizophrenia although effective are not perfect as they might be associated with different side effects. (…)* The use of treatment with new mechanism of action may exert some risks, which, based on available information, was recognized and the study was design to minimize it.** **"This phase II study is to evaluate the efficacy, safety and tolerability and PK of 2 doses of CPL500036, compared to placebo in patients with an acute exacerbation of schizophrenia. (…)* Patients 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 will be excluded from the study and risk of potential suicide ideations occurrence will be assessed during the study."** **full text available in 2.5 section*
4.2. Scientific Rationale for the Study Design	The following text has been added: **"The study design meets the recommendations provided in the "Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia" (EMA/CHMP/40072/2010 Rev. 1, 30). (…)* Extrapyramidal symptoms (EPS) are potential adverse events that according to guideline are to be monitored during the studies in schizophrenia patients, which was addressed by using ESRS scale for EPS monitoring."** **full text available in 4.2 section*
Rationale: Minor errors were noted	
5.4.1. Dietary and Fluid Restrictions	The following text has been modified: "Dosing Day: Dosing during treatment period will take place after an overnight fast of at least 10 hours. Water intake will be allowed up to 1 hour before dosing and from ~~**2**~~ **1 hours** after dosing (excluding amount of water allowed for IMP administration).
5.4.3. Prior and Concomitant Treatments	The following text has been modified: "Patients will not be eligible for the study if they have used any depot antipsychotic within ~~**one treatment cycle prior to Day −1**~~ **1 month**

	(30 days) prior to Screening. ~~**or have used**~~ **The using of** mianserin, mirtazapine, nefazadone, cyproheptadine, or fluvoxamine within **1 month** (30 days) ~~**prior to the Day -1**~~ **before Screening is not recommended**."
11.5. Informed Consent	The following text has been modified: "As part of the informed consent procedure, the Investigator must explain orally and in writing the nature, duration and purpose of the study and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences or AEs that may occur. The subject should be informed that he/she is free to withdraw from the study at any time. Subjects will receive all information that is required by ~~**federal**~~ **local** regulations and ICH guidelines."
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Rationale: The additional clarification was added	
5.4.3. Prior and Concomitant Treatments	The following text has been added: **"Allowed concomitant medications taken by the patient in fasting conditions can be taken consistently with the current recommendations, but at least 1 hour interval between concomitant medication and IMP administration must be maintained with IMP taken as first."**
6.8. Blinding and Breaking the Blind	The following text has been modified: "The study blind ~~**should not**~~ **may** be broken ~~**except**~~ **only in** ~~**from**~~ medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency). The decision to break the blind will be made on a case-by-case basis, at the discretion of the Investigator, **and if possible**, in collaboration with the Sponsor and/or Medical Monitor."
6.9. Treatment of Overdose	The following text has been added: "Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. **The patient's conditions will be constantly monitored by Investigator. Each case of overdose will be reported immediately to the Sponsor. The Investigator should follow-up and document the course and the outcome of each overdose even if the subject was withdrawn from the clinical study or if the clinical study has finished and if the patient agrees. Any SAE that occurs due to overdose must be recorded on the Serious Adverse Event Report Form and must be reported by Investigator to the Sponsor within 24 hours of becoming aware of the event."**
7.1. Study Stopping Rules	The following text has been added:

	"If the Investigator, the Medical Monitor or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. **If the investigator considers, that the continuation of the study is a "possible hazard" to the specific subject or the risk-benefit considerations have changed, the Investigator may decide the termination of the study for this subject without the consent/consulting Sponsor.** The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding."
7.1.1.1. Safety Criteria	The following text has been added: "An individual subject is to be withdrawn from the study if: • the subject requires treatment with any medication known or suspected to interfere with the study medication **in the opinion of the Investigator or designee"**
7.2. Subject Withdrawal and Replacement	The following text has been added: "The subject who withdraws from the study for any reason after any IMP administration or before completion the study, may be replaced by another qualifying alternate only in case if total number of subjects in a given study arm who would complete the study would be insufficient and there are no safety concerns. **The subject replacement is defined as recruiting additional patient, but it should be remembered that results from all randomized patients will be analyzed according to the population set definitions described in section 10.1.3."**
11.8 Confidentiality Data protection	The following text has been modified: "The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name, **or by subject number and birth year only, if required and to comply with local data protection regulations**. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Investigator."
Rationale: The section was adjusted to clarify and specify allowed concomitant medication usage (in accordance with the Hungarian Regulatory Authority recommendations).	
5.4.3. Prior and Concomitant Treatments	The following text has been modified: **"**In addition, benzatropine/**biperiden** may be administered for treatment of extrapyramidal side effects and propranolol may be administered for treatment of akathisia. Lorazepam, zolpidem, benzatropine/**biperiden** and propranolol are allowed according to the instructions outlined in Table 5 below. Within the daily **and weekly** limits shown in Table 5, lorazepam, zolpidem, benzatropine/**biperiden,** and propranolol are **permitted upon the Investigator or designee decision and** are ~~**NOT**~~ allowed on a PRN (as needed) basis~~**; each and every administration must be**

	~~**considered and approved by the Investigator prior to administration.**~~ **If the patient's condition will require administration of higher dose of lorazepam, zolpidem, benzatropine/biperiden, or propranolol (exceeding the limits given in Table 5), it must be recorded as Serious Adverse Event (SAE).** The adverse event (AE) associated with the need for lorazepam, zolpidem, benzatropine/**biperiden,** or propranolol should be recorded on the AE eCRF. The amount and timing of each lorazepam, zolpidem, benzatropine/**biperiden**, or propranolol administration should be recorded for each patient in the eCRF.**"**
5.4.3. Prior and Concomitant Treatments	The table 5 was modified, as follows: -determine of weekly limits -akathisia treatment update
13.Appendices	The table 9 was modified, as follows: -update according to section 5.4.3.
Rationale: Deletion of the confusing record without any substantial changes in statistics	
10.3. Primary Efficacy Analysis	The following text has been modified: "The null hypothesis is that there is no difference in the primary endpoint between either dose group compared to placebo, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 10% significance level. The primary endpoint will be analysed using a mixed effect repeated measures model (MRMM), with treatment and timepoint as fixed effects and baseline score as a covariate. 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. A sensitivity analysis will be conducted whereby missing data is imputed using multiple imputation. The primary analysis will compare each dose group with placebo. ~~**without adjustment for multiplicity. As a secondary analysis of the primary endpoint a comparison of both treatment groups pooled, compared to placebo will also be made."**~~
Rationale: Addition of new references (due to extension of explanation in section 2.5. and in section 4.2.)	
12. Reference List	The following references were added: **"28. Kinon, B. J., Potts, A. J., & Watson, S. B. (2011). Placebo response in clinical trials with schizophrenia patients. *Current opinion in psychiatry*, *24*(2), 107-113.**

	29. Oliveira, I. R. D., Nunes, P. M., Coutinho, D. M., & Sena, E. P. D. (2009). Review of the efficacy of placebo in comparative clinical trials between typical and atypical antipsychotics. *Brazilian Journal of Psychiatry*, *31*(1), 52-56. **30. "Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia" (EMA/CHMP/40072/2010 Rev. 1)"**

AMENDMENT 2 – Protocol v. 2.0 dated 28 August 2020 → Protocol v. 2.1 dated 21 December 2020	
Applicable Section	**Description of Change(s)**
Rationale: Minor errors were noted	
1.1. Protocol synopsis, Study population, Inclusion criteria	The following text has been modified: "6. A female is eligible to participate if she is not pregnant (negative pregnancy ~~**serum**~~ test at Screening and Day -1), not breastfeeding, and at least 1 of the following conditions applies:"
5.2. Inclusion criteria	The following text has been modified: "6. A female is eligible to participate if she is not pregnant (negative pregnancy ~~**serum**~~ test at Screening and Day -1), not breastfeeding, and at least 1 of the following conditions applies:"
1.1. Protocol synopsis, Study population, Exclusion criteria	The following text has been modified: "6. The patient has a moderate or severe substance use disorder (meeting more than ~~**5**~~ **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."
5.3. Exclusion criteria	The following text has been modified: "6. The patient has a moderate or severe substance use disorder (meeting more than ~~**5**~~ **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."
Rationale: Clarifying note was added	
1.1. Protocol synopsis, Criteria for evaluation	The following text has been modified: "Blood samples for PK analysis will be collected at the following time points for extensive PK sampling (approximately 30% of patients): • Day 1 and Day 7 (steady state): pre-dose and 0.5, 1, 1.5, 2, 4, 8, 12, and 24* hours post-dose. • Days 2 to 6: pre-dose* and around 2 hours post-dose. • Day 28: pre-dose and around 2 hours post-dose. ***please note – the sample 24 hours post-dose on Day 1 it is the same sample as pre-dose on Day 2."***
1.3. Schedule of Assessments, Footnotes for Table 1	The following text has been modified: "j) For patients undergoing extensive PK sampling, blood samples for PK analysis collected on Day 1 and Day 7 will be collected pre-dose and 0.5, 1, 1.5, 2, 4, 8, 12, and 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 be collected pre-dose* and around 2 hours post-dose. ***please note – the sample 24 hours post-dose on Day 1 it is the same sample as pre-dose on Day 2."***

8.4.1. Blood sample collection	The following text has been modified: "Blood samples for PK analysis will be collected at the following time points for extensive PK sampling (approximately 30% of patients): • Day 1 and Day 7 (steady state): pre-dose and 0.5, 1, 1.5, 2, 4, 8, 12, and 24* hours post-dose. • Days 2 to 6: pre-dose* and around 2 hours post-dose. • Day 28: pre-dose and around 2 hours post-dose. ***please note – the sample 24 hours post-dose on Day 1 it is the same sample as pre-dose on Day 2."***

AMENDMENT 1 – Protocol v. 1.0 dated 29 May 2020 → Protocol v. 2.0 dated 28 August 2020	
Applicable Section	**Description of Change(s)**
Rationale: change of dose after Regulatory Authority recommendations.	
1.1. Protocol synopsis, Study Design	The following text has been modified: "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** ~~**60**~~ mg CPL500036 or placebo."
1.1. Protocol synopsis, Study Design	The following text has been modified: "During the Treatment Period, patients will be dosed with 20 mg CPL500036, **40** ~~**60**~~ 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."
4.1 Study design, Overview	The following text has been modified: "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** ~~**60**~~ mg CPL500036 or placebo." Additionally, the following text has been modified on the same page: "During the Treatment Period, patients will be dosed with 20 mg CPL500036, **40** ~~**60**~~ 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."
4.3. Justification for Dose	The following text has been modified: "In Part B of the Phase I, subjects were divided into four cohorts. During the fourteen days, every cohort took other doses of the IMP: 3 mg, 10 mg, 30 mg and 60 mg. All doses were tolerated well by subjects and were generally safe. Even at the highest dose, the IMP cause only the transient adverse events assessed as mild or moderate. For this reason, the Sponsor decided to administer two doses in the Phase II: 20 mg and **40** ~~**60**~~ mg. Further details can be found in the IB [23]."
6.6 Dosing	The following text has been modified:" To maintain double-blind manner, every patient will take the same number of capsules. Depending on the dose (20 mg or **40** ~~**60**~~ mg) and the type of product (PG20 or placebo) intended for patient, he/she will take: - **4** ~~**6**~~ capsules of PG20: **40** ~~**60**~~ mg, - 2 capsules of PG20 and **2** ~~**4**~~ capsules of placebo: 20 mg, - **4** ~~**6**~~ capsules of placebo."

6.7. Compliance, IMP accountability	The following text has been modified:" Dosing will be performed by trained, qualified personnel designated by the Investigator. A hand and mouth check will be performed after dosing to ensure the subjects have swallowed the dose administered. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures. A single dose is to be considered as a compliant when all **4** ~~**6**~~ capsules are administered and administration is without any emesis occurring within 2h after IMP administration. A patient is to be considered as compliant with dosing regimen when at least 80 % of the doses are compliant (at least 22 doses)."
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
APO	Apomorphine
ASST	Attentional set shifting task
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve from time zero to 24 hours
BACS	Brief Assessment of Cognition in Schizophrenia
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
b.w.	Body weight
cAMP	cyclic adenosine monophosphate
CAR	Conditioned Avoidance Response
CGI-I	Clinical Global Impression Scale - Improvement
CGI-S	Clinical Global Impression Scale- Severity
cGMP	cyclic guanosine monophosphate
CL/F	Apparent clearance
C_{max}	Maximum observed concentration
CRF	Case report form
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	Observed trough concentrations
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	electronic case report form

ED	Extra-dimensional
EDC	Electronic data capture
EPS	Extrapyramidal side effects
ESRS	Extrapyramidal Symptom Rating Scale
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRMM	Mixed effect repeated measures model
MSN	Medium spiny neurons
NOAEL	No-observed-adverse-effect-level
NOR	Novel object recognition test
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PD	Pharmacodynamics
PDE10A	Phosphodiesterase 10A
PK	Pharmacokinetics
PP	Per Protocol Set
PPI	Pre-pulse inhibition of the acoustic startle response
PRN	As needed
PS	Pharmacokinetic Set
QTcF	QT interval corrected for heart rate using Fridericia’s correction

SAE	Serious adverse event
SCID-5-CT	Structured Clinical Interview for DSM-5 Clinical Trial Version
SD	Standard deviation
SID	Subject identification
SOC	System organ class
SOP	Standard operating procedure
SS	Safety Set
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent terminal elimination half-life
t_{max}	Time corresponding to occurrence of C_{max}
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during terminal phase

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title	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
Study Numbers	Sponsor Protocol No.: 02PDE2019
Development Phase	Phase II
Sponsor	Celon Pharma S.A.
Study Centers	This study will be conducted at multiple clinical units.
Study Objectives	**Primary Objective:** **Efficacy:** • To determine if CPL500036 administered for 28 days can attenuate the positive symptoms associated with schizophrenia. **Secondary Objectives:** **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). **Safety:** • To assess the safety and tolerability of CPL500036 administered for 28 days. **Pharmacokinetics:** • To assess the pharmacokinetic (PK) profile of CPL500036 administered for 28 days.
Study Design	This is a double-blind, randomized, placebo controlled, parallel group, dose ranging study to explore the efficacy, safety, tolerability and PK of 2 different doses of CPL500036 (phosphodiesterase 10A [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 randomization on Day 0. 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.
Investigational Medicinal Product	CPL500036 will be supplied by the Sponsor as PG20 product capsules with 10 mg of CPL500036 as an active pharmaceutical ingredient (API), in blister packs. The matching placebo will be supplied by the Sponsor as capsules matching the PG20 product capsules, in blister packs.
Number of Subjects	Approximately 165 patients.
Study Population	**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 years 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. **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 patients 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: o A serum creatinine value > 1.5 times the upper limit of normal (ULN). o A total serum total bilirubin value > 1.5*ULN. o A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value > 2*ULN. **NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening and on Day -1. If a patient status after screening changes at baseline (Day -1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). It should be remembered

	that all baseline procedures must be performed on Day -1, but final patient qualification should be made when all results are available, before randomization on Day 0.

Criteria for Evaluation	**Efficacy:** *Primary Endpoint:* • Change from baseline in PANSS positive subscale at Week 4. *Secondary Endpoints:* • 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]. **Safety:** *Secondary Endpoints:* • Physical, neurological, ophthalmological, and dermatological examination findings. • Adverse event assessments. • Hematologic, clinical chemistry, coagulation and urinalysis results. • Electrocardiogram (ECG) results. • **Pharmacokinetics:** *Secondary Endpoints:* The data permitting the following plasma PK parameters will be evaluated after single and multiple dose administration for the extensive and sparse PK sampling group: • Maximum observed concentration (C_{max}) • Time corresponding to occurrence of C_{max} (t_{max}) • AUC from time zero to 24 hours (AUC_{0-24}) • Apparent terminal elimination half-life ($t_{1/2}$) • Apparent clearance (CL/F) • Apparent volume of distribution during terminal phase (V_z/F) • Concentration immediately prior to dosing (C_{trough}). This parameter will only be calculated during the multiple dose administration.

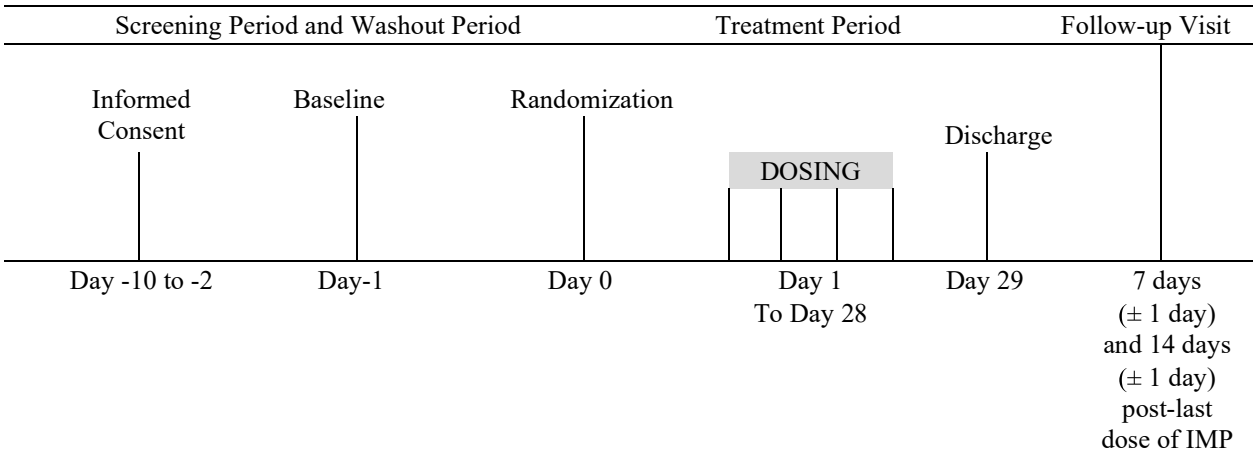
	Blood samples for PK analysis will be collected at the following time points for extensive PK sampling (approximately 30% of patients): • Day 1 and Day 7 (steady state): pre-dose and 0.5, 1, 1.5, 2, 4, 8, 12, and 24* hours post-dose. • Days 2 to 6: pre-dose* and around 2 hours post-dose. • Day 28: pre-dose and around 2 hours post-dose. **please note – the sample 24 hours post-dose on Day 1 it is the same sample as pre-dose on Day 2.* Blood samples for PK analysis will be collected at the following time points for sparse PK sampling (approximately 70% of the patients): • Day 1 and Day 7 (steady state): pre-dose and 1, 2, 4 and 8 hours post-dose. • Day 28: pre-dose and around 2 hours post-dose.
Statistical Methods	**Sample Size Considerations:** 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). **Data Presentation/Descriptive Statistics:** *Analysis Sets:* • 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 Set (SS): All patients who received at least 1 dose of study treatment (either CPL500036 or placebo). • Pharmacokinetic Set (PS): All subjects in the safety set with at least 1 evaluable PK parameter. • Pharmacokinetic Set for parameter calculation (PSPC): All subjects 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. *Evaluation of Efficacy:* Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis for the

	respective treatment group. For continuous variables, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. For all analyses data from all centres will be pooled. *Primary Efficacy Analysis:* The null hypothesis is that there is no difference in the primary endpoint between either dose group compared to placebo, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 10% significance level. The primary endpoint will be analysed using a mixed effect repeated measures model (MRMM), with treatment, time point, clinical site and interaction between clinical site and timepoint as fixed effects and baseline score as a covariate. If there will be many clinical sites with few subjects, they can be pooled into bigger groups. 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. A sensitivity analysis will be conducted whereby missing data is imputed using multiple imputation. The primary analysis will compare each dose group with placebo, based on estimated marginal means (aka least square means, LS-means) from the model without adjustment for multiplicity. As a secondary analysis of the primary endpoint a comparison of both treatment groups pooled, compared to placebo will also be made. *Secondary Efficacy Analyses:* All secondary endpoints will be analysed without adjustment for multiplicity. The secondary endpoints, which are continuous, will be analysed using the same approach as described for the primary endpoint. Missing data will be assumed to be missing at random. At each time point, 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) will be analysed at each time point using a Logistic regression model with treatment and clinical site (or country if there will be many clinical sites) as a fixed effect and baseline score as a covariate. If a patient is missing data in order to derive their response at a given time point, the missing data will be imputed using multiple imputation for continuous endpoints and non-responser imputation for binary endpoints prior to the analysis. *Pharmacokinetic and PK/PD Analyses:* Evaluation of Pharmacokinetics CPL500036 plasma concentrations will be listed and summarized descriptively and graphically by time point and treatment group. Pharmacokinetic parameters of CPL500036 will be listed and summarized. Pharmacokinetic/PD data will also be displayed graphically as appropriate. *Safety Analyses:* Evaluation of Safety endpoints will be summarized descriptively by treatment group and visit for the Safety Population.

1.2. Schema

The study design is presented in Figure 1.

Figure 1 Study Overview



IMP = investigational medicinal product

1.3. Schedule of Assessments, Time Points and Window Allowance

Details on procedures and timing of assessments are presented in Table 1.

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**		**Wee**
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**22 to 27**
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	X
Resumption of anti-psychotics											
Safety and Tolerability:											
Adverse event questioning	X	X		X	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**		**Wee**
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**22 to 27**
Study Plan											
ESRS monitoring [d]	X	X		X		X		X		X	
Prior/concomitant medication	X	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	
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										

	Screening Period [a] and Washout Period [b]	Baseline and Washout [b]	Randomization[b]	Treatment Period							
Study Week				**Week 1**			**Week 2**		**Week 3**		**Wee**
Study Day	**-10 to -2**	**-1**	**0**	**1**	**2 to 6**	**7**	**8 to 13**	**14**	**15 to 20**	**21**	**22 to 27**
Study Plan											
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]			
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: Electrocardi
Symptom Rating Scale; CGI-I: Clinical Global Impression Scale - Improvement; CGI-S: Clinical Global Impression Scale -
Medicinal Product; PANSS: Positive 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
etc.).

b) Patients that fulfil all the inclusion criteria and none of the exclusion criteria will then be admitted to the Clinical Unit on
Wash-out Period of up to 7 days (Day -7 to Day -1) before the randomization on Day 0. The duration of the Medication Wa
omitted for 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); onc 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 a BACS); once during 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 s minutes before or after 2h post-dose (it will be performed after PANSS, CGI-S, CGI-I, BACS and ESRS); once during the

f) Respiratory rate, body temperature, 3-positional blood pressure and pulse (after 3 minutes lying down; after 3 minute sittir and after 3 minutes standing) will be taken once at Screening (Day -10 to -2); once at Baseline (Day -1); thrice on Day 1, predose (≤ 1h before IMP administration) and within 5 minutes before or after 1h 45 minutes and 9h post-dose; once durir

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 (≤ once during 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 r dose (it will be 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 of r before or 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-S and CGI-I).

j) For patients undergoing extensive PK sampling, blood samples for PK analysis collected on Day 1 and Day 7 will be colle 4, 8, 12, and 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 be 2 hours 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 coll 8 hours post-dose.

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

2. INTRODUCTION

2.1. Background

Phosphodiesterase 10A (PDE10A) is an enzyme belonging to the phosphodiesterase's' family consisting of 11 members [1]. PDE10A possesses several splice variants not differing in the catalytic domain [2]. PDE10A is expressed highly specific in the striatum [3], in particular in medium spiny neurons (MSNs). MSNs compose about 90% of the striatum and are characterized by expression of either dopamine receptors D1 or D2 that allow to group them in 2 different projection circuits. MSNs expressing D1 receptors project to substantia nigra and constitute striatonigral (direct) pathway. MSNs characterized by D2 expression project to globus pallidus and comprise striatopallidal (indirect) pathway. These 2 pathways have contrary action on the transmission enabling to regulate various functions involved in control of motor movement, cognitive processes, emotions and learning [4].

PDE10A hydrolyses both cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) – cyclic nucleotides that are secondary messengers in many types of cells [1]. cAMP and cGMP in MSNs may trigger various molecular events including phosphorylation of the Protein Kinase A (PKA), Protein Kinase G (PKG), exchange proteins directly activated by cAMP (Epacs) and cyclic nucleotide-gated ion channels (CNG) [5]. Downstream signalling includes phosphorylation and activation of proteins that are highly expressed in MSNs – in particular: dopamine and cyclic AMP-regulated phospho- protein (DARPP-32) – as well activation of MAPK/ERK pathway. Thus, inhibition of the PDE10A may modulate the MSNs action in an efficient way. Inhibition of PDE10A in the stratopallidal circuit leads to diminishing of the D2 activation signalling in contrast to the direct circuit, where stratonigral inhibition of the PDE10A result in mimicking the D1 signalling [6]. Balance between these 2 circuits plays essential function in controlling motor and executive functions [7]. It is postulated that modulation of both circuits by inhibition of PDE10A may lead not only to treating the positive symptoms, but also to improving negative or cognitive dysfunctions in schizophrenia [8]. These effects have been shown in several preclinical models by use of various PDE10A inhibitors [9; 10; 11; 12].

CPL500036 is a novel, PDE10A inhibitor characterized by high in vitro potency and selectivity. CPL500036 has good oral bioavailability and blood-brain-barrier penetration in rats. Several behavioural studies have confirmed its antipsychotic and pro-cognitive action in rats. *Ex vivo* studies have confirmed dose dependent phosphorylation of proteins dependent on cyclic nucleotides concentrations. Based on the preclinical studies the compound has been selected as a good clinical candidate for the treatment of schizophrenia and psychotic disorders.

The compound CPL500036 was initially developed as a hydrochloride salt. This form was used for preclinical studies including non-good laboratory practice (non-GLP) toxicity studies for determination of maximum tolerated dose and no-observed-adverse-effect-level (NOAEL) dose during 14-day toxicity study in rats and dogs. However, due to instability of the salt caused by release of the hydrochloride and constituently changing water content, free form of the compound was selected for remaining toxicity studies in GLP standard - 28-days administration study in rats and dogs.

The final product PG20 that was used in phase I clinical trial contains CPL500036 in free form as an active pharmaceutical ingredient (API) with excipients: copovidone, crospovidone, mannitol. Final product differs from the product (formulation) used in toxicity studies. To compare both formulations bridging PK studies in rats and dogs were performed. In both species the formulations presented a comparable PK profile with minimal higher exposition for the final product (30% higher exposition based on $AUC_{(0-t)}$ for the doses around determined NOAELs).

Celon Pharma's product PG20, with CPL500036 as an active ingredient was designed predominantly for the treatment of psychotic disorders like schizophrenia. There are also some literature background information's suggesting that PDE10 inhibitors may have a beneficial effect for a patient suffering from Levodopa-induced dyskinesia in Parkinson's disease and/or Huntington's disease.

Schizophrenia is a mental disorder seriously impairing the ability to think logically, establish relationships with people and functioning in society [13]. This disease affects about 1% of the population with the onset of morbidity at the age of 20 to 30 years. It is characterized by many symptoms, which in each patient can develop in a completely different direction and occur with various intensities. For this reason, it could be diagnosed even after several years of illness [14]. The risk of developing schizophrenia is closely related to the individual possibilities of coping with stress and emotions. In the development of the disease, the importance of genetic background was found. Schizophrenics revealed morphological changes in the structure of the brain, abnormalities in size, distribution and the mutual connection of neurons in the brain. Schizophrenia is characterized by the presence of positive symptoms (auditory hallucinations, delusions, hallucinations) and negative symptoms (concentration disorders, apathy, social withdrawal, impoverishment of vocabulary and hypomimia) [15]. The exact causes of schizophrenia are still under investigation, however, the leading hypotheses base on the high or low abundance of specific neurotransmitters: dopamine and glutamate, respectively [16]. Therefore, psychotic episodes may be controlled, and in many cases prevented, by treatment with dopamine D2 receptor antagonists. These antipsychotic agents represent the first and only line of

pharmacotherapy for the treatment of schizophrenia and have significantly reduced the burden of this illness on patients and society. However, the use of anti-psychotics can be associated with severe, mechanism-related motor side effects, and 10% to 30% of patients receive little or no benefit from D2 receptor antagonists [13]. Although newer, atypical agents with mixed pharmacology have an improved safety profile with respect to motor side effects, many of them are associated with metabolic effects that can result in serious de novo medical problems. Moreover, there is a consensus that neither typical nor atypical agents treat the debilitating negative and cognitive symptoms of schizophrenia in the sufficient degree.

2.2. Summary of Findings from Non-clinical Studies with Potential Clinical Relevance

The purpose of the *in vivo* studies presented below was the examination of the CPL500036 effects on the positive, negative and cognitive schizophrenia symptoms in various pharmacological rat models.

2.2.1. *In Vivo* Behavioural Studies – Antipsychotic Effects

To assessed CPL500036 potential antipsychotic effects three *in vivo* behavioural studies were performed:

Conditioned Avoidance Response:

The Conditioned Avoidance Response (CAR) test allows to identify drugs having particular tranquillizing properties that are specifically effective against psychotic symptoms [17].

Inhibition of induced hyperlocomotion using phencyclidine and apomorphine models:

In this study CPL500036 was evaluated as an antipsychotic agent in a pharmacological model of psychosis – phencyclidine (PCP) and apomorphine (APO) induced hyperlocomotion paradigm. In humans, PCP and APO are known to produce a syndrome of behavioral effects which have many characteristics in common with schizophrenia [18]. Therefore, antagonism of PCP and APO effects might be evidence for antipsychotic efficacy of a compound.

Pre-pulse inhibition of the acoustic startle response:

Pre-pulse inhibition of the acoustic startle response (PPI). PPI is a neurological phenomenon in which a weaker pre-stimulus (pre-pulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse). On a loud acoustic stimulus, normal rats (and humans) display a startle response [19]. The presentation of a pre-pulse stimulus reduces startle. Compounds that model certain aspects of psychoses reverse this reduction; this effect can be normalized by many anti-psychotics.

Different doses of CPL500036 was tested. Minimal effective doses achieved at mentioned studies as well as all tested doses are summarized in Table 2.

Table 2 The minimal effective doses (MED) and all tested doses of CPL500036 administered to rats in behavioral tests assessing potential antipsychotic effects

Test		Species	Tested doses [mg/kg b.w.]	MED [mg/kg b.w.]
Antipsychotic effect	Conditioned avoidance response (CAR)	Rat	0.1	0.2
			0.2	
			0.3	
	Inhibition of phencyclidine induced hyperlocomotion (PCP- induced HA)	Rat	0.1	0.1
			0.3	
			1	
			3	
			10	
	Inhibition of apomorphine induced hyperlocomotion	Rat	0.3	0.6
			0.6	
	Prepulse inhibition of the acoustic startle response (PPI)	Rat	0.1	0.3
			0.3	

b.w. = body weight

The results of presented behavioral studies in rats suggest antipsychotic-like activity of CPL500036 compound from 0.1 mg/kg body weight.

2.2.2. *In Vivo* Behavioural Studies – Pro-cognitive Effects

To assessed CPL500036 potential pro-cognitive effects three *in vivo* behavioral studies were performed:

Novel object recognition:

For evaluation of pro-cognitive effect of CPL500036, the novel object recognition test (NOR) was performed. The NOR task is very useful to study working memory and is evaluated by the differences in the exploration time of novel and familiar objects. Normal rats show reduced exploration of the novel object at short time; compounds that disturb learning (PCP, ketamine, scopolamine) produce lack of object discrimination. Conversely, normal rats show similar exploration of the known and novel objects at long; pro-cognitive compounds like PDE10A inhibitors may reduce the exploration of the familiar object.

Attentional set shifting task:

The attentional set shifting task (ASST) was developed as a measure of attention and cognitive flexibility in rats [20]. The ability to learn simple rules remains intact, deficits in learning to modify a response when the rules have changed are found in patients suffering from a variety of neuropsychiatric disorders such as schizophrenia.

In ASST paradigm, rats must select a bowl containing a food reward based on the ability to discriminate the odours or the media covering the bait. The ASST requires rats to initially learn a rule and form an attentional “set” within the same stimulus dimensions. At the extra- dimensional (ED) shift stage, the essential phase of the task, animals must switch their attention to a previously irrelevant stimulus dimension and, for example, discriminate between the odours and not between the media covering the bait. The animal's performance at the ED stage is considered an index of cognitive flexibility.

Five-choice serial reaction time task:

Executive functions, such as attention and inhibitory control, are affected in many psychiatric disorders, e.g. schizophrenia, attention-deficit hyperactivity disorder (ADHD) and substance abuse disorders. The 5-choice serial reaction time task (5-CSRTT) for rats, in which the animals have to respond to a brief stimulus presented pseudo-randomly in 1 of 5 holes in order to obtain a food reward and which measures aspects of visuospatial sustained and divided attention, as well as a form of impulsive action called ‘waiting impulsivity’ [21].

Different doses of CPL500036 was tested. Minimal effective doses achieved at mentioned studies as well as all tested doses are summarized in Table 3.

Table 3 The minimal effective doses (MED) and all tested doses of CPL500036 administered to rats in behavioral tests assessing potential procognitive effects

Test		Species	Tested doses [mg/kg b.w.]	MED [mg/kg b.w.]
Procognitive effect	Novel object recognition test (NOR)	Rat	0.03	0.1
			0.1	
			0.3	
	Attentional set shifting task (ASST)	Rat	0.01	0.03
			0.03	
			0.1	
	Five-choice serial reaction time task (5-CSRTT)	Rat	0.03	0.1
			0.1	

b.w. = body weight

The results of presented behavioral studies in rats suggest pro-cognitive effect of CPL500036 compound from 0.03 mg/kg body weight.

2.2.3. *In Vivo* Behavioural Studies – Effects on Negative Symptoms of Schizophrenia

To assessed CPL500036 potential effects on negative symptoms one *in vivo* behavioural study was performed:

Social interaction test:

Social interactions are a fundamental and adaptive component of the biology of numerous species. Social recognition is critical for the structure and stability of the networks and relationships that define societies. Specifically, perturbations in social functioning such as social withdrawal and asociality that represent key items of a cluster of negative symptoms of schizophrenia may be modelled using the social interaction test (SIT) [22].

Different doses of CPL500036 was tested. Minimal effective dose was not achieved at mentioned study. All tested doses are summarized in Table 4.

Table 4 The minimal effective doses (MED) and all tested doses of CPL500036 administered to rats in behavioral tests assessing effects on negative symptoms

Test		Species	Tested doses [mg/kg b.w.]	MED [mg/kg b.w.]
Negative symptoms	Social interaction test (SIT)	Rat	0.1	ND
			0.3	
			0.6	

b.w. = body weight; ND = not determined

CPL500036 at tested doses did not improve the negative-like symptoms of schizophrenia as assessed in a model based on N-Methyl-D-aspartate (NMDA) receptor antagonist–induced social withdrawal.

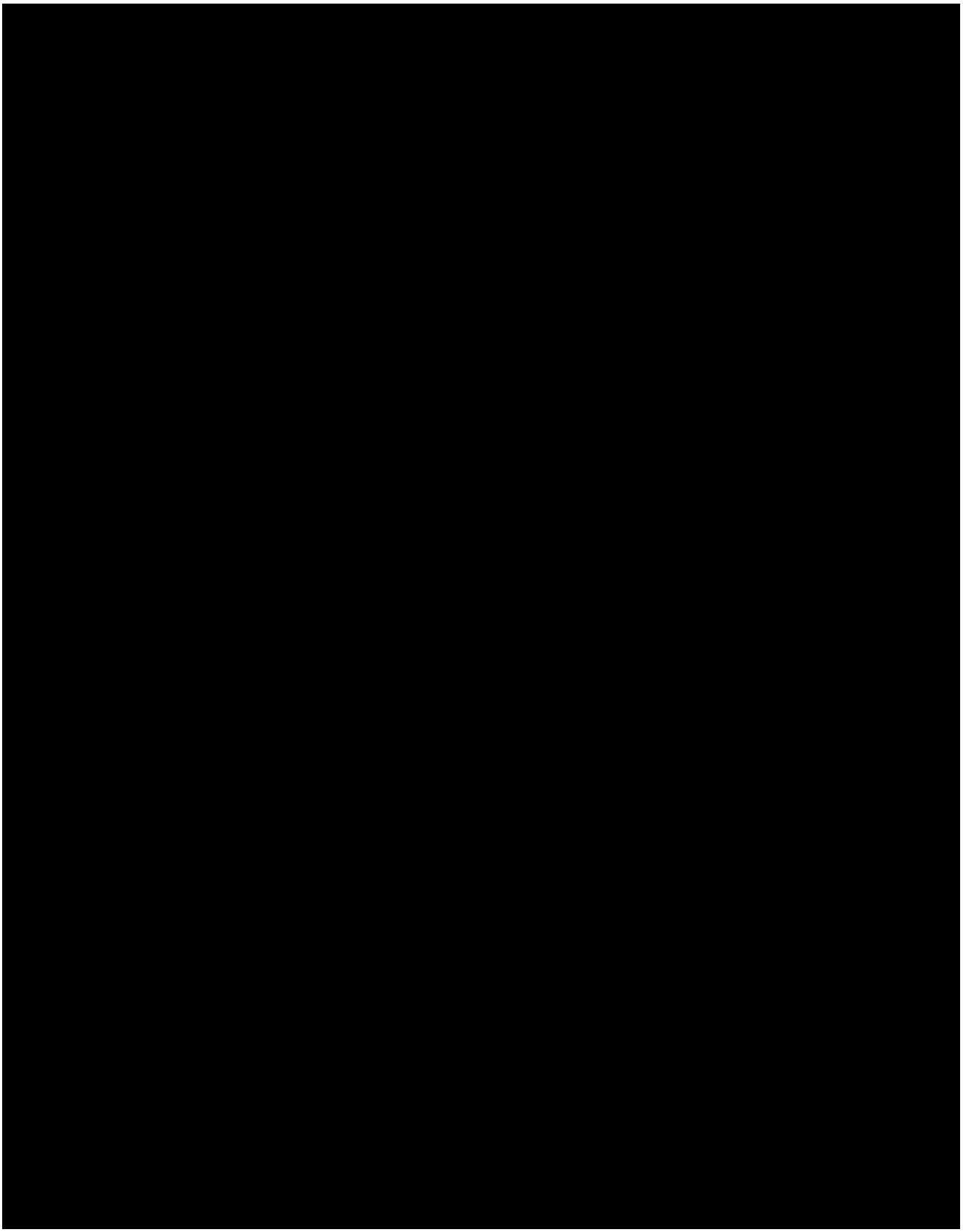
Further details can be found in the Investigator's Brochure (IB) [23].

2.2.4. Toxicology

[redacted]

2.3. Summary of Findings from Previous Clinical Studies

[redacted]



[redacted]

2.4. Rationale for the Clinical Study

[redacted]

[redacted]

2.5. Risk-benefit Assessment

Current antipsychotics used in patients with schizophrenia although effective are not perfect as they might be associated with different side effects. The development of new, effective therapy with improved safety profile would be a beneficial treatment options for schizophrenia patients. The PDE10 inhibitors, based on several preclinical models, may represent a new approach for treatment of psychosis. The use of treatment with new mechanism of action may exert some risks, which, based on available information, was recognized and the study was design to minimize it.

In a similar phase 2, randomized, placebo-controlled study, the efficacy and safety of a selective PDE10A inhibitor (TAK-063) in patients with an acute exacerbation of schizophrenia were evaluated [25]. In this study, no clinically relevant or consistent differences were observed between study drug and placebo groups for hematologic, renal, or hepatic lab test results, vital signs, or ECG. Most subjects reported AEs that were mild or moderate in severity, and the AEs reported in this study were generally consistent with the previously conducted phase 1 studies [26, 27]. AEs experienced by ≥5% of subjects in the IMP (TAK-063) group were akathisia (placebo: 4.9%; IMP: 13.3%), somnolence (placebo: 2.5%; IMP: 12.0%), dyspepsia (placebo: 7.4%; IMP: 10.8%), headache (placebo: 11.1%; IMP: 7.2%), nausea (placebo: 6.2%; IMP: 6.0%), dystonia (placebo: 1.2%; IMP: 6.0%), and decreased appetite (placebo: 1.2%; IMP: 6.0%). None of the serious adverse event (SAE) was considered related to study drug. The investigated PDE10A inhibitor did not result in any deaths, and most AEs were mild or moderate in severity and did not result in the specific study discontinuation [26, 27].

Phase I study results in healthy volunteers showed that CPL500036 compound is generally safe and well tolerated. Potential risks associated with use of CPL500036 based on most frequently AE occurrence in phase I study, assessed as related or possible related with IMP:

- Drowsiness/somnolence,
- Feeling calm,
- Headache,
- Sensation of cold,
- Sensation of hot/heat.

The intensity of observed AEs was classified as mild or moderate. All the AEs were transient and their frequency decreased after Day 3 of administration (in multiple dosing). The most

frequent AE were drowsiness and somnolence (more than 50% all AEs reported in PART B). Details can be found in the IB [23].

This phase II study is to evaluate the efficacy, safety and tolerability and PK of 2 doses of CPL500036, compared to placebo in patients with an acute exacerbation of schizophrenia.

Preclinical results available for CPL500036 compound shows antipsychotic-like properties of the compound. The potential attenuation of positive symptoms associated with schizophrenia, in patients receiving the IMP, will be evaluated. Treatment efficacy will be tested with potential improvements at the higher doses. Placebo patients will not receive active treatment so should not experience health benefits. However, patient receiving placebo may show improvement, called the placebo effect, since higher placebo response is observed in patients with schizophrenia clinical studies in the last decades [30]. In the Takeda's phase II study with TAK-063, PDE10 inhibitor, mentioned above, percentages of responders were approximately 43% or 29% of patients receiving placebo, based on PANSS or CGI-I score, respectively [25].

The use of placebo in clinical studies with schizophrenia patients raise some ethical concerns. However as stated in the "Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1, 30). the use of placebo control is considered necessary for assay sensitivity and when "safeguards are in place the benefits of using a placebo arm will generally override any ethical reservations in short term controlled efficacy trials". Placebo control group is required by many regulators because of its importance in helping to identify safety signals in clinical trial [28]. Placebo-controlled trails are usually consider the gold standard method to prove efficacy and safety of new drugs, including antypsychotics [29]. An apparent paradox occurs in placebo-controlled studies. Using placebo challenges the ethical aspects but the use of placebo in drug development may actually serve to reduce the overall number of patients who are exposed to ineffective treatments because those studies require smaller sample size to detect a significant difference [28]. Thus, due to relative small number of patients included in randomized, placebo studies, consequently the number of non-responders are small. Studies involving placebo in psychosis are short in duration (maximum of eight weeks) and based on the evidence available, the conventional antipsychotics are associated with only a small effect when administered this short, with the larger effect in long-term studies [29]. Moreover, psychotic patients in placebo-controlled studies are usually hospitalized, under constant supervision. They receive medications to control anxiety, agitation and insomnia and treatment may be discontinued if ineffective. Due to this some may argue that hospitalized psychiatric patients using placebo are not in fact receiving "no treatment". Even the hospitalization itself may largely contribute with recovery [29].

The 02PDE2019 study is considered a short term study with up to 7 days of medication washout period and 28-day treatment phase. The CPL500036 compound will be used in monotherapy , so other antipsychotic treatments will be discontinued, what is in line with the EMA guidelines which states that "treatments that may augment the test treatment should be excluded, despite the consequences of these exclusions for generalizability of the trial results. Therefore other antipsychotic drugs should be discontinued (…)" [30]. The protocol has been designed to minimize the risk to all research participants. This study will be performed in controlled settings, all patients will be hospitalized to assure patients safety. Subjects will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs.

To manage potential side effects and symptoms that may occur, allowed treatments are described. During the study lorazepam may be administered for anxiety/agitation or to aid sleep. To manage insomnia from z-drugs, use of zolpidem is allowed in the study. To treat extrapyramidal side effects and akathisia benzatropine/biperiden and propanolol are permitted, respectively. The daily and weekly limits of those medications that can be used, on a PRN (as needed) basis are provided (rules for medication administration in Section 5.4.3). If a patient's condition will require to exceed the specified dose, it must be recorded as Serious Adverse Event.

During the whole study all the patients will be closely observed by the Investigator or appointed staff members to assure maximal safety. Safety is to be ensured by performing clinical assessments/ evaluations and clinical laboratory measurements/ evaluations. This includes i.a. monitoring of vital signs with 3-positional blood pressure and pulse measurements, ECG measurements and extrapyramidal side effects monitoring using Extrapyramidal Symptom Rating Scale (ESRS) assessments. Patients 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 will be excluded from the study and risk of potential suicide ideations occurrence will be assessed during the study.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

Efficacy:

- To determine if CPL500036 administered for 28 days can attenuate the positive symptoms associated with schizophrenia.

3.2. Secondary Objectives

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).

Safety:

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

Pharmacokinetics:

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

3.3. Endpoints

3.3.1. Efficacy

Primary Endpoint:

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

Secondary Endpoints:

- 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].

3.3.2. Safety

Secondary Endpoints:

- 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).

3.3.3. Pharmacokinetics

Secondary Endpoints:

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_{0-24})
- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution during terminal phase (V_z/F)
- Concentration immediately prior to dosing (C_{trough}). This parameter will only be calculated during the multiple dose administration.

4. STUDY DESIGN

4.1. Overview

This is a double-blind, randomized, placebo controlled, parallel group, dose ranging study to explore the efficacy, safety, tolerability and PK of 2 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 randomization on Day 0. 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.

4.2. Scientific Rationale for the Study Design

This study evaluates the efficacy, safety, tolerability and PK of 2 different doses of CPL500036 (PDE10A inhibitor) in patients with an acute exacerbation of schizophrenia. The design is standard and is considered appropriate to meet the objectives of the study.

The study design meets the recommendations provided in the "Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia" (EMA/CHMP/40072/2010 Rev. 1, 30). This is a proof-of-concept study assessing CPL500036 compound with new mechanism of action in treating positive symptoms of schizophrenia so comparison to placebo is considered appropriate to assess treatment benefit. To better characterize the effect size two doses of CPL500036 as monotherapy will be used. Risks in the study, especially those of using placebo were acknowledge and the study was design to minimize it (see section 2.5). For efficacy assessment validated scales recommended in the guideline are to be used as an assessment tools. PANSS will be used for primary endpoint measurements, including the recommended definition of responders used in short term trials with acute/exacerbated symptoms is to be used for clinical response evaluation. For secondary efficacy measures both CGI-S and CGI-I assessments are planned in the study. Extrapyramidal symptoms (EPS) are potential adverse events that according to guideline are to be monitored during the studies in schizophrenia patients, which was addressed by using ESRS scale for EPS monitoring.
The safety assessments for the study are accepted measures for ensuring safety of subjects during a clinical trial. The PK sampling schedule is considered appropriate given the information available. The rationale for dose selection is discussed in Section 4.3.

4.3. Justification for Dose

[redacted]

4.4. Order of Assessments

The following priority order will be in effect when more than one assessment is required at a pre-dose and post-dose time point, with PK blood sampling being performed in the specified time:

1. Vital signs,

2. 12-lead ECG,
3. Blood sampling for safety and PK assessments,
4. PANSS, CGI-S, CGI-I and BACS,
5. ESRS monitoring,
6. Columbia Suicide Severity Rating Scale (C-SSRS).

4.5. Study Duration

The duration of participation for each subject will be approximately 8 weeks. The estimated study duration includes:

7. Screening Period: Up to 10 days.
8. Treatment Period: Days 1 to 28.
9. Follow-up Period: 7 to 14 days after the post-last dose of IMP (Day 28) – Days 35 to 42.

4.6. End of the Study

For the entire study, end of the study is defined as the last visit of the last subject for any protocol related activity (last subject, last visit). -

4.7. Study Completion

A subject is to be considered to have completed the double-blind treatment phase if he/she has completed all the assessments and procedures on Day 28. Subject who, for any reason, discontinues the study before Day 28 is not to be considered to have completed the study.

4.8. Early Termination

If a subject withdraws prematurely after dosing, all data normally collected at discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge. If deemed necessary by the Investigator, the subject will be asked to return for an unscheduled visit for safety follow-up.

5. STUDY POPULATION

The study population will consist of male and female patients with an acute exacerbation of schizophrenia. Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and on Day -1. If a patient status after screening changes at baseline (Day -1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). It should be remembered that all baseline procedures must be performed on Day -1, but final patient qualification should be made when all results are available, before randomization on Day 0.

5.1. Number of Subjects

A total of 165 subjects will be enrolled in the clinical study.

5.2. 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.

5.3. 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.

5.4. Restrictions

5.4.1. Dietary and Fluid Restrictions

Caffeine

Xanthine containing products (e.g., caffeine in coffee, tea, chocolate) will not be allowed from 24 hours prior to Day 1 to Day 28, inclusive. Subjects should not consume caffeine containing beverages exceeding 500 mg caffeine per day (5 cups of coffee) during the off-site days during the study.

Alcohol

Consumption of alcohol and alcohol-containing foods, medications or beverages must be avoided from 48 hours prior to Day -1 and while subjects are confined to the study center. Subjects should not consume more than 3 units (males) or 2 units (females) per day during the study Follow-up period (1 unit is equal to approximately ½ pint [284 mL] of beer, one small glass [125 mL] of wine, or one measure [25 mL] of spirits).

Meals

No outside food or drink is permitted at the study center. During in-house stay at the study center only meals and fluid intake according to the study center's meal plan will be allowed.

Fasting

Dosing Day: Dosing during treatment period will take place after an overnight fast of at least 10 hours. Water intake will be allowed up to 1 hour before dosing and from 1 hour after dosing (excluding amount of water allowed for IMP administration).

After IMP administration patients should remain fasting:

- On Day 1, Days 2-6, Day 7 and Day 28: up to 2 hours,
- On every other day: up to 2h but starting from 0.5h after IMP administration consumption of low calorie snack i.e. plain rice cakes is allowed till breakfast.

5.4.2. Lifestyle Considerations

Drugs of abuse

Subjects must refrain from use of recreational drugs for the duration of the study.

Nicotine

Cigarette smokers will be allowed to smoke in designated areas provided by the clinic and the number of cigarettes per day should be recorded. The number of cigarettes will be limited to a maximum of 20 per day. No smoking will be allowed 90 minutes before efficacy testing.

Strenuous activity

Subjects should refrain from carrying out heavy physical training (e.g., long distance running, weight-lifting, or any physical activity to which the subject is not accustomed) from 48 hours prior to Day -7 – Day -1 (depending if/ how long washout period is included) until the final Follow-up Visit. Subjects should neither start any new physical training nor increase the intensity of their usual training during study participation. Subjects may participate in light recreational activities during studies (e.g., watch television, play computer games, read).

5.4.3. Prior and Concomitant Treatments

Medication restrictions applicable before dosing are described in Section 5.3 (exclusion criteria). Prior medication will be recorded.

Any medicinal product, prescribed or over-the-counter (OTC), taken by a subject other than the IMP, is considered concomitant medication. Permitted medication (for prolonged use) includes only paracetamol in recommended doses (≤ 2 g per day) after approval by the Investigator or designee. Higher doses of paracetamol, up to 4 g per day may be given at the discretion of the

Investigator or designee to treat AEs such as fever and headache (only for short terms issues). Any concomitant treatment will be given only if deemed strictly necessary by the Investigator or designee. Use of concomitant medication will be recorded and reported.

Allowed concomitant medications taken by the patient in fasting conditions can be taken consistently with the current recommendations, but at least 1 hour interval between concomitant medication and IMP administration must be maintained with IMP taken as first.

Starting on the first day of Screening Period and as applicable, all antipsychotic or other psychotropic medications will be stopped with clinically appropriate titration down as per Investigator clinical judgment. Thereafter, patients will be instructed not to take any medications during the conduct of the study unless approved by the Investigator. Any patient who is unable to be safely discontinued from current antipsychotic therapy or other psychotropic medications will not be eligible for the study (see Section 7).

Medication history (psychotropic medication history during the previous 5 years and all other medications during the past 12 months) will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

Patients will not be eligible for the study if they have used any depot antipsychotic within 1 month (30 days) prior to Screening. The using of mianserin, mirtazapine, nefazadone, cyproheptadine, or fluvoxamine within 1 month (30 days) before Screening is not recommended.

During the study lorazepam may be administered for anxiety/agitation or to aid sleep; from other medications to manage insomnia, known as z-drugs, zolpidem is preferred and allowed. Lorazepam and zolpidem are not to be used in close temporal proximity (administration within 4h of each other). In addition, benzatropine/biperiden may be administered for treatment of extrapyramidal side effects and propranolol may be administered for treatment of akathisia. Lorazepam, zolpidem, benzatropine/biperiden and propranolol are allowed according to the instructions outlined in Table 5 below. Within the daily and weekly limits shown in Table 5, lorazepam, zolpidem, benzatropine/biperiden, and propranolol are permitted upon the Investigator or designee decision and are allowed on a PRN (as needed) basis.

If the patient's condition will require administration of higher dose of lorazepam, zolpidem, benzatropine/biperiden, or propranolol (exceeding the limits given in Table 5), it must be recorded as Serious Adverse Event (SAE).

The adverse event (AE) associated with the need for lorazepam, zolpidem, benzatropine/biperiden, or propranolol should be recorded on the AE eCRF. The amount and timing of each lorazepam, zolpidem, benzatropine/biperiden, or propranolol administration should be recorded for each patient in the eCRF.

Table 5 Restrictions on the Use of Lorazepam, Zolpidem, Benzatropine/Biperiden, and Propranolol during the Study

<table>
<tr><th>Medication</th><th>Study Period</th><th>Dosage Allowed</th><th>Timing Restrictions</th></tr>
<tr><td rowspan="3">Lorazepam</td><td rowspan="2">Screening Period and Treatment Period to Day 28, inclusive</td><td>Maximum of 6 mg/day
AND</td><td rowspan="3">Not within 8 hours prior to PANSS, CGI-S, CGI-I or C-SSRS, BACS
Not within 4 h of zolpidem administration</td></tr>
<tr><td>Maximum 6 times/week
(at least 1 day break between weeks)</td></tr>
<tr><td>Follow up period – Since Day 29 and onwards</td><td>According to SmPC</td></tr>
<tr><td rowspan="3">Zolpidem</td><td rowspan="2">Screening Period and Treatment Period to Day 28, inclusive</td><td>Maximum of 10 mg/day</td><td rowspan="3">Not within 8 hours prior to PANSS, CGI-S, CGI-I or C-SSRS, BACS
Not within 4 h of lorazepam administration</td></tr>
<tr><td>Maximum 4 times/week</td></tr>
<tr><td>Follow up period – Since Day 29 and onwards</td><td>According to SmPC</td></tr>
<tr><td>Benzatropine</td><td rowspan="2">Screening Period to Day 28, inclusive</td><td>Maximum of 4 mg/day</td><td rowspan="3">Not within 8 hours of BACS, ESRS</td></tr>
<tr><td>Biperiden</td><td>According to SmPC</td></tr>
<tr><td>Propranolol</td><td>Screening Period to Day 28, inclusive</td><td>Maximum of 40 mg/day</td></tr>
</table>

BACS: Brief Assessment of Cognition in Schizophrenia; C-SSRS: Columbia Suicide Severity Rating Scale; CGI-I: Clinical Global Impression Scale - Improvement; CGI-S: Clinical Global Impression Scale - Severity; PANSS: Positive and Negative Syndrome Scale

A list of example medications that are allowed and not allowed as concomitant medications for either episodic or chronic use is provided in Table 9 in the Appendices (Section 13).

Strong inducers and inhibitors of CYP3A4 should be avoided due to possible effects on the pharmacokinetics of CPL500036 (PDE10A inhibitor), however, moderate to weak inducers or inhibitors may be allowed.

Precaution should be exercised in patients using concomitant treatment with agents being BCRP (Breast Cancer Resistance Protein) substrates (e.g. ezetimibe, pravastatin, rosuvastatin), as the Investigational Product may inhibit the BCRP. As per Table 9, the dose of these drugs should be stable within 1 month prior to Screening to allow objective patient's follow up. Any confusions related to the changes in patient's status and/or laboratory results should be discussed with the Medical Monitor.

5.4.4. Contraception Rules

Refer to Section 5.2 (inclusion criteria).

6. INVESTIGATIONAL MEDICINAL PRODUCT

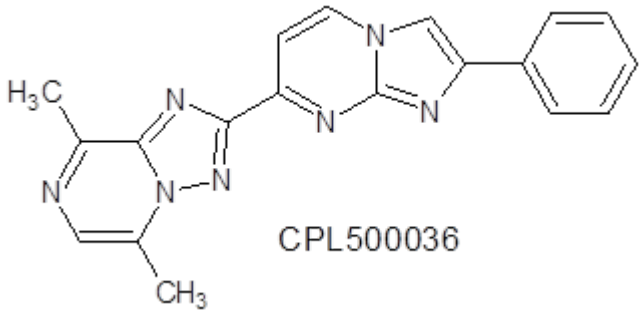
6.1. Study Agent

6.1.1. Physico-chemical characteristics

Active substance: CPL500036

Chemical name: 7-5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl}-2-phenylimidazo[1,2-a]pyrimidine

Chemical structure:



CPL500036

Molecular formula: C19H15N7

Molecular weight: 341,37 g/mol

6.1.2. Formulation

[redacted]

Table 6 The composition of powder filled into gelatin capsule.

[redacted]

6.2. Identity of the Investigational Medicinal Products

[redacted]

6.3. Supply, Packaging, Labelling and Storage

[redacted]

6.4. Subject Identification and Randomization

6.4.1. Screening Numbers

At Screening, subjects will be assigned a unique subject identification number (or subject identifier). Enrolled subjects who drop out of the clinical study before randomization will retain their subject identification number.

6.4.2. Randomization Numbers

Prior to dosing, on Day 0, subjects will be assigned a randomization number in accordance with the randomization code generated by eCRF platform. Randomization procedure is to be performed to minimize bias in the assignment of subjects to treatment groups. Subjects are to be randomized in 1:1:1 ratio (a stratified block is to be implemented: geographical location, PK group, PANSS baseline score).

Once a randomization number has been allocated to one subject, it may not be assigned to another subject.

6.5. Administration of Investigational Medicinal Products

Starting from Day 1, the IMP will be administered after a minimum 10-hours overnight fast with approximately 240 mL water. Subjects must remain in an upright position for at least 2 hours after dosing. The IMP is to be administered approximately at the same time each day.

Fasting requirement after IMP intake are described in Section 5.4.1.

For dosing details, see Section 6.6 below.

6.6. Dosing

To maintain double-blind manner, every patient will take the same number of capsules. Depending on the dose (20 mg or 40 mg) and the type of product (PG20 or placebo) intended for patient, he/she will take:

- 4 capsules of PG20: 40 mg,
- 2 capsules of PG20 and 2 capsules of placebo: 20 mg,
- 4 capsules of placebo.

In this way, both the patient and the Investigator will not know which product is administered to the patient.

6.7. Compliance, IMP accountability

Dosing will be performed by trained, qualified personnel designated by the Investigator. A hand and mouth check will be performed after dosing to ensure the subjects have swallowed the dose administered. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures. A single dose is to be considered as a compliant when all 4 capsules are administered and administration is without any emesis occurring within 2h after IMP administration. A patient is to be considered as compliant with dosing regimen when at least 80 % of the doses are compliant (at least 22 doses).

The Sponsor shall supply an adequate quantity of the investigational medicinal product (IMP) and the placebo, both for administration and as a backup, along with the respective certificates of analysis (CoA). Appropriate sealing of packages with the IMP/placebo and adequacy of the information included on the package labels is to be examined by the designated unblinded study person (pharmacist) in the clinical centre. The amount of each product is to be sufficient to account for any loss resulting from its potential damage or subject's withdrawal. The unblinded persons are obliged to store the products in a safe place, with limited access to third parties. The products are to be securely stored under pre-specified conditions, in accordance with applicable regulatory requirements. The products are to remain under the supervision of the designated study person and are to be released solely for the administration purposes, according to the study protocol. The study designated person is to be responsible for the investigational product during the whole study period. At the end of the study, a number of unused IMP is to be determined, and the product is to be returned to the Sponsor along with used containers. Adequate records documenting receipt, use or other disposition of the investigational product is to be kept by the designated person. The unblinded study monitor is to verify these documents throughout the course of the study.

6.8. Blinding and Breaking the Blind

The clinical study will be performed in a double-blind manner, so the identity of investigational drug and placebo will not be known to investigators, research staff and subjects. At the Clinical Units are to be at minimum two staff members, who are to be unblinded: pharmacist preparing the products to be administered based on randomization list and one person from the team who is to be responsible for verifying the proper preparation of the product doses (quality control). They are not to be involved in any evaluation and examination of the study patients. The unblinded staff members are obligated not to share the randomization list with other staff members during the whole study. The adequate pharmaceutical manual is to be prepared by the clinical units and is to be followed.

The study blind may be broken only in medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency). The decision to break the blind will be made on a case-by-case basis, at the discretion of the Investigator, and if possible, in collaboration with the Sponsor and/or Medical Monitor. If the blind is broken the CRO and Sponsor must be informed as soon as possible. The date, time and reason for unblinding is to be documented in the CRF and in the source data. The applicable standard operating procedure (SOP) will be followed for blind breaking procedures.

After database lock, the overall randomization code will be broken only for reporting purposes.

Suspected unexpected serious adverse reactions (SUSARs), that are subject to expedited reporting, should be unblinded by the Sponsor before submission to the regulatory authority and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Information about SUSAR should be sent to all Investigators too (after unblinding the patient).

6.9. Treatment of Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. The patient's conditions will be constantly monitored by Investigator. Each case of overdose will be reported immediately to the Sponsor. The Investigator should follow-up and document the course and the outcome of each overdose even if the subject was withdrawn from the clinical study or if the clinical study has finished and if the patient agrees. Any SAE that occurs due to overdose must be recorded on the Serious Adverse Event Report Form and must be reported by Investigator to the Sponsor within 24 hours of becoming aware of the event.

7. DISCONTINUATION

7.1. Study Stopping Rules

The stopping rules described in this section of the clinical study protocol (CSP) are applicable to stopping the study. IMP dosing may be halted temporarily to investigate before the entire study is terminated.

Measures to ensure data integrity and safety of research subjects will be detailed in the Safety Monitoring Plan (SMP) and Data Management Plan (DMP).

If the Investigator, the Medical Monitor or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. If the investigator considers, that the continuation of the study is a "possible hazard" to the specific subject or the risk-benefit considerations have changed, the Investigator may decide the termination of the study for this subject without the consent/consulting Sponsor. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.

Should the study be terminated, and/or the study centre closed for whatever reason, all documentation pertaining to the study and study drug must be returned to the Sponsor. Any actions of the contract research organization (CRO) required for assessing or maintaining subject safety will continue as required, despite termination of the study by the Sponsor.

7.1.1. Stopping Rules

7.1.1.1. Safety Criteria

After the first dose of IMP, a subject may discontinue from the study for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other reasons, as determined by the Investigator. If a subject discontinues treatment, their participation in the trial will be discontinued. Discontinued subjects should be encouraged to complete all early termination and Follow-up assessments with early termination assessments conducted as soon as possible after the subject is withdrawn.

An individual subject is to be withdrawn from the study if:

- the subject withdraws his/her consent, what he/she is allowed to do at any time and without the need to justify his/her decision,

- the subject requires treatment with any medication known or suspected to interfere with the study medication in the opinion of the Investigator or designee
- the subject is no longer able to participate for other medical reasons (e.g. surgery, adverse event),
- the subject – in spite of the earlier evaluation upon recruitment – is suspected or found not to comply with eligibility criteria,
- there is evidence or sound suspicion that the subject fails to comply with the protocol directives (compliance with the treatment schedule, non-adherence to dietary rules or other study restrictions that may have influence on study results, non-attendance at study assessments),
- or any other condition occurs which in the opinion of the Investigator no longer justifies or permits a safe participation of the subject.

Each subject has the right to withdraw from the study at any time without prejudice. The Principal Investigator may discontinue any subject's participation when he/she feels it is necessary, for any reason including adverse events or Clinical Study Protocol violation. The subject is to be always informed about the reason for his discontinuation. Reasons for the withdrawal of an individual subject from the study are to be recorded by the Investigator in the Case Report Form and in the Clinical Study Report. In the case of withdrawal caused by adverse drug reaction, the subject is to be under observation until symptoms of the reaction have subsided.

In case of emesis an individual subject is to be withdrawn from the study if:

- the subject suffers from severe emesis within 4 hours after two consecutive days of drug administration. If emesis occurs within 4 hours post-dose and is to be mild or moderate or emesis occurs after 4 hours post-dose, discontinuation of the subject depends on Investigator's judgement and decision.

7.2. Subject Withdrawal and Replacement

In addition to the stopping rules described in Section 7.1.1, a subject will be withdrawn by the Investigator or designee from the study and not be allowed to continue with the study if any of the following criteria are fulfilled:

- If discovered that the subject has entered the study in violation of the inclusion/exclusion criteria stated in the protocol,

- Investigator or the Sponsor stops the study, for any reason (e.g., suspension or discontinuation of study drug development).

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any subject withdraws from the study prematurely. All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge.

Subject participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event,
2. Protocol violation,
3. Loss to follow-up,
4. Subject withdrew consent at own request,
5. Other.

A genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. At least 3 documented attempts of telephone contacts must be documented by the site. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject requesting him/her to contact the clinic.─In case of failure, patient is considered lost to follow up.

The subject who cannot participate in the study due to not meeting the inclusion or exclusion criteria or is going to withdraw the informed consent before the first IMP administration is to be replaced by the next qualifying alternate.

The subject who withdraws from the study for any reason after any IMP administration or before completion the study, may be replaced by another qualifying alternate only in case if total number of subjects in a given study arm who would complete the study would be insufficient and there are no safety concerns. The subject replacement is defined as recruiting additional patient, but it should be remembered that results from all randomized patients will be analyzed according to the population set definitions described in section 10.1.3.

The replacing subject is to follow the same treatment and protocol procedures as the withdrawn one. The replacing alternate subject is to receive the study products under the same conditions as the withdrawn subjects, and they are to undergo the entire protocol procedure.

8. STUDY ASSESSMENTS AND PROCEDURES

For timing of assessments, refer to the Schedule of Assessments (Table 1).

8.1. Eligibility Screening

For patient eligibility screening assessments and procedures, please refer to Schedule of Assessments (Table 1).

8.2. Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history,
- Medication history,
- Reproductive history.

The following demographic information will be recorded:

- Age,
- Race/ethnicity,
- Height, without shoes (cm),
- Body weight, without shoes (kg),
- Body mass index (BMI) (kg/m^2).

Other baseline characteristics will be recorded as follows:

- History of drug abuse,
- History of alcohol abuse,
- Smoking history,
- Special diet (e. g. vegetarian),
- History of blood or plasma donation.

8.3. Safety Variables

8.3.1. Adverse Events

Adverse event reporting will begin for each subject from the date the informed consent form (ICF) is signed and will continue until the final Follow-up Visit.

8.3.1.1. Definitions

8.3.1.1.1. Definition of Adverse Event

Any untoward medical occurrence in a subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g. those occurring during treatment-free periods (including Screening or post-treatment follow-up periods), in association with study-related procedures and assessments, or under placebo. For study drugs, lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way, e.g., greater in severity.

Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the Treatment Period. Pre-existing conditions will be recorded as part of the subject's medical history.

8.3.1.1.2. Definition of Serious Adverse Event

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe,
- Requires in-patient hospitalization or prolongation in existing hospitalization,
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Is a congenital anomaly/birth defect, or
- Is another important medical event (see below).

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures

that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered a SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily a SAE. For example, alopecia may be assessed as severe in intensity but would not be considered a SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

8.3.1.2. Recording of Adverse Events

Adverse events should be collected and recorded for each subject from the date the ICF is signed until the end of their participation in the study, i.e. the subject has discontinued or completed the study.

Adverse events may be volunteered spontaneously by the subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.3.1.3. Assessment of Adverse Events

Each AE will be assessed by the Investigator about the categories discussed in the following sections.

8.3.1.3.1. Intensity

The Investigator will assess all AEs for severity in accordance with the following standard ratings.

- Mild: Ordinarily transient symptoms, does not influence performance of subject's daily activities. Treatment is not ordinarily indicated.
- Moderate: Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary.
- Severe: Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.

8.3.1.3.2. Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the categories described in Table 7 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 7 Assessment of Relationship of Adverse Events to Investigational Product

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge*) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge† procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

*Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are

exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

†Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

8.3.1.4. Reporting of Serious Adverse Events

The Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to study drug. All SAEs will be recorded from signing of the ICF until the final Follow-up Visit. Serious AEs occurring after the final Follow-up Visit and coming to the attention of the Investigator must be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the study drug.

The Investigator is responsible for providing notification to the Sponsor of any SAE, whether deemed IMP-related or not, that a subject experiences during their participation in study within 24 hours of becoming aware of the event.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS
Notify and send the SAE Report Form and any supporting documentation via email within 24 hours of becoming aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number,
- Patient number,
- Sex,
- Date of birth,
- Name of Investigator and full clinical site address,
- Details of SAE,
- Criterion for classification as ‘serious’,
- Study drug name, or code if unblinded, and treatment start date,
- Date of SAE onset,
- Causality assessment (if sufficient information is available to make this classification).

The Sponsor will request clarification of omitted or discrepant information from the initial notification. The Investigator or an authorized delegate is responsible for sending via email the requested information to the Sponsor within 24 hours of the Sponsor's request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g. hospital reports, consultant reports, autopsy reports), with the subject's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and emailed to the Sponsor within 24 hours of receipt of the information. If a new SAE report form is emailed, then the Investigator must sign and date the form. The Sponsor may also request additional information on the SAE, which the Investigator or an authorized delegate must send via email to the Sponsor within 24 hours of the request.

8.3.1.5. Reporting of Suspected Unexpected Serious Adverse Reaction

Information on SUSARs will be collected and reported to the regulatory authority and the IEC in accordance with European Commission Guidance 2011/C 172/01 or as per national regulatory requirements in the participating country. Details of reporting on country level will be described in the Safety Management Plan.

8.3.1.6. Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

8.3.1.7. Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy new-born should not be considered a SAE.

Each pregnancy must be reported by the Investigator to the Sponsor within 2 days after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the

outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has finished and if the patient agrees.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor on the pregnancy outcome report form within 2 days after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Report Form(e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

8.3.2. Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected at the time points detailed in the Schedule of Assessments (Table 1). During administration days samples will be collected pre-dose (≤ 1h before IMP administration). Samples will be collected in appropriate tubes and handled according to standard procedures of the applicable laboratory.

Clinical laboratory variables will be determined as outlined in Table 8.

Table 8 Clinical Laboratory Assessments

Hematology	
White blood cell (WBC) count	Neutrophils (percentage and absolute count)
Red blood cell (RBC) count	Lymphocytes (percentage and absolute count)
Hemoglobin (Hb)	Monocytes (percentage and absolute count)
Hematocrit (HCT)	Eosinophils (percentage and absolute count)
Mean corpuscular volume (MCV)	Basophils (percentage and absolute count)
Mean corpuscular hemoglobin (MCH)	Platelet count
Mean corpuscular hemoglobin concentration (MCHC)	RBC distribution width
Coagulation	
Prothrombin time (PT)	International Normalized Ratio (INR)
Activated partial thromboplastin time (aPTT)	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Gamma glutamyl transferase (GGT)
Albumin	Glucose
Alkaline phosphatase (ALP)	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Phosphorus
Blood urea nitrogen (BUN)	Potassium
Calcium	Sodium
Chloride	Total bilirubin
Cholesterol	Total protein
Creatinine	Triglycerides
Creatine kinase (CK)	Uric acid
Follicle stimulating hormone (FSH) (Screening Visit only; all female subjects)	
Urinalysis	
Bilirubin	Blood
Glucose	pH and specific gravity
Ketones	Protein
Leukocytes	Urobilinogen
Nitrite	
Microscopic (only for abnormal urine stick test findings)	
Viral Serology	
Hepatitis B surface antigen (HBsAg)	Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies
Hepatitis C virus antibody (anti-HCV)	
Urine Drug Screening	
Amphetamines	Cocaine
Barbiturates	Opiates
Benzodiazepines	Phencyclidine (PCP)
Cannabinoids	
Pregnancy Testing	
Serum/urine human beta chorionic gonadotrophin (women of childbearing potential only)	

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the Screening Period is indicated as clinically significant, the subject will not be allowed to be enrolled into the study without permission of the Medical Monitor and Sponsor. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality in laboratory tests is found during the course of treatment period study, and/or at the final Follow-up Visit, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Investigator.

8.3.3. Alcohol test

An estimation of blood alcohol content from a breath sample or from an urine sample is to be performed to determine if subject is not under influence of alcohol.

8.3.4. Vital Signs

Vital signs will be assessed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

Respiratory rate (breaths per minute), body temperature (°C), 3-positional blood pressure (systolic and diastolic [mmHg]) and pulse (beats per minute [bpm]) (after 3 minutes lying down; after 3 minute sitting, immediately upon standing; and after 3 minutes standing) will be taken taken once at Screening (Day -10 to -2); once at Baseline (Day -1); thrice on Day 1, Days 2-6 (each day), Day 7, 14, 21 and 28: pre-dose (≤ 1h before IMP administration) and within 5 minutes before or after 1h 45 minutes and 9h post-dose; once during the follow-up visits .

8.3.5. Standard 12-lead Electrocardiograms

Standard safety 12-lead ECGs will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below. The ECGs will be performed once, pre-dose (≤ 1h before IMP administration) at all scheduled visits when IMP is administered.

- Once at Screening (Days -10 to -2) and at Baseline (Day -1),
- On Days 7, 14, 21 and 28: pre-dose,
- On Follow-up Visits (Days 35 to 42).

The12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes. The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval and QTc interval (QT interval corrected for heart rate using QTcF).

All ECGs must be evaluated by a qualified designee for the presence of abnormalities.

8.3.6. Physical Examinations

Physical examinations will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

- at Screening (Days -10 to -2) and at Baseline (Day -1),
- On Day 28; not earlier than 5h post-dose,
- On Follow-up Visits (Days 35 to 42).

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic and psychiatric systems) will be performed.

8.3.7. Extrapyramidal Side Effects

Extrapyramidal side effects monitoring will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

Extrapyramidal side effects will be monitored starting from Screening, Baseline, and on Day 1 , Day 7, Day 14, Day 21, Day 28 and follow-up visits, using the Extrapyramidal Symptom Rating Scale (ESRS). ESRS was developed to assess four types of drug-induced movement disorders (DIMD): Parkinsonism, akathisia, dystonia, and tardive dyskinesia.

ESRS to be conducted during IMP administration days, 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).

8.3.8. Columbia Suicide Severity Rating Scale

Columbia Suicide Severity Rating Scale is a suicidal ideation rating scale created by researchers at Columbia University to evaluate suicide risk. Questions are phrased for use in an interview format, but the C-SSRS may be completed as a self-report measure if necessary. The scale contains

6 “yes” or “not” questions. An individual exhibiting even a single behaviour identified by the scale was 8 to 10 times more likely to commit suicide.

CSSRS will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

Columbia Suicide Severity Rating Scale will be conducted starting from Screening, baseline, on Day 14 and Day 28, and during the follow-up visits,. The C-SSRS should be done AFTER all efficacy and safety assessments/scales.

8.3.9. Additional Safety Variables

Basic neurological, ophthalmological and dermatological assessment will be performed by Investigator. In case of a need, consultation with specialist may be considered and it remains at the Investigator’s discretion.

Neurological, ophthalmological, and dermatological examinations will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

Neurological examinations:

- At Screening (Days -10 to -2) and at Baseline (Day -1),
- On Days 7, 14, 21 and 28; not earlier than 5h post-dose,
- On Follow-up Visits (Days 35 to 42).

Ophthalmological examinations:

- At Screening (Days -10 to -2) and at Baseline (Day -1),
- On Day 28 not earlier than 5h post-dose.

Dermatological examinations:

- At Screening (Days -10 to -2) and at Baseline (Day -1),
- On Day 28; not earlier than 5h post-dose.

8.4. Pharmacokinetics Variables

8.4.1. Blood Sample Collection

Blood for the analysis of CPL500036 will be collected at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below.

Blood samples for PK analysis will be collected at the following time-points for extensive PK sampling (approximately 30% of patients):

- Day 1 and Day 7 (steady-state): pre-dose and 0.5, 1, 1.5, 2, 4, 8, 12, and 24* hours post-dose,
- Days 2 to 6: pre-dose* and around 2 hours post-dose,
- Day 28: pre-dose and around 2 hours post-dose.

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

Blood samples for PK analysis will be collected at the following time-points for sparse PK sampling (approximately 70% of the patients):

- Day 1 and Day 7 (steady state): pre-dose and 1, 2, 4 and 8 hours post-dose,
- Day 28: pre-dose and around 2 hours post-dose.

Blood samples are to be collected according to the presented schedule, with the allowable deviation of ± 1 minute for the first 2 h, ± 2 minutes for 4-12 h and ± 30 minute for 24 h post-dose.

Blood samples are to be collected, centrifuged, processed and stored for analysis in accordance with bioanalytical laboratory specified procedure, which is to be provided before the start of the study.

8.5. Efficacy Variables

The efficacy will be assessed by using various psychometric scales. Every scale will be performed by experienced and trained raters (certified in PANSS scale) according to planned schedule of assessments.

8.5.1. Positive and Negative Syndrome Scale

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.

Positive and Negative Syndrome Scale will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

The efficacy assessment (PANSS) will be performed once at Screening (Day -10 to -2); once at Baseline (Day -1); on Days 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 before any other scale).

8.5.2. Clinical Global Impression Scale - Severity

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; it is often used both before and after treatment. Scores on the Severity of Illness subscale range from 1 = not ill at all to 7 = among the most extremely ill.

Clinical Global Impression Scale - Severity will be performed at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

The efficacy assessment (CGI-S) will be performed once at Screening (Days -10 to 2), once at baseline (Day -1); on Days 7, 14, 21 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (after PANSS).

8.5.3. Clinical Global Impression Scale - Improvement

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 at the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

The efficacy assessment (CGI-I) will be performed on Days 7, 14, 21 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (after PANSS and CGI-S)

8.5.4. Brief Assessment of Cognition in Schizophrenia

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 the time points detailed in the Schedule of Assessments (Table 1) and as detailed below:

The BACS assessment will be performed at Baseline (Day -1) and on Days 14 and 28 when start of ratings is to be within 5 minutes before or after 2h post-dose (after PANSS, CGI-S and CGI-I)..

8.6. Total Amount of Blood

The maximum volume of blood planned for collection from each subject over the course of the entire study (from the Screening Visit to the final Follow-up Visit, but not including repeat or additional tests ordered by the Investigator) will not exceed 500 ml and presents no undue risk to the subjects.

8.7. Hospitalization

Patients are to be hospitalized after the screening qualification for washout period of up to 7 days (if necessary) before the start of the 28-day Treatment Period. Patients are to be hospitalized during the treatment period (Day 1 to Day 28). On Day 29 patients may be discharged from the clinical centre based on local standards of care if the patient is in stable condition under the regular medication(s).

9. STUDY SCHEDULE

9.1. Screening

Before providing the potential study patient with the information leaflet and informed consent form, the physician responsible for the enrollment provides them detailed information on:

- The purpose of the study,
- Any potential risk and inconveniences associated with the study, among others the number of visits and all study procedures that are to be performed,
- Patient's responsibilities (restrictions, sampling schedule etc.),
- Right to refuse to participate or withdraw from the study at any time,
- Confidentiality of patient's medical information,
- Person to contact for further information regarding the study and whom to contact in case of any side effects occur,
- Expected duration of the patient's participation in the study,
- Entities granted direct access to the patient's original medical records for verification of clinical study procedures.

The potential patient is to be given enough time to make a fully conscious and informed decision to participate in the study.

After obtaining the written Informed Consent Form signed and dated by the patient Screening procedures as detailed in the Schedule of Assessments (Table 1) are to be performed. For description of these procedures see Sections 8.3.2 - 8.3.9 and for all of the inclusion/exclusion criteria patients must meet see Sections 5.2 and 5.3.

Patients will undergo screening assessments from Day -10 to Day – 8 in multiple settings (i.e. emergency departments, outpatient clinics etc.). Patients that fulfil all the inclusion and none of the exclusion criteria will immediately be admitted to the Clinical Unit and enter Medication Washout Period of up to 7 days (Day -7 to Day -1) before treatment phase, if needed. The duration of Medication Washout Period may be shorter or omitted for non-medicated patients.

Approximately 165 patients who meet all of the inclusion and none of the exclusion criteria are to be enrolled into the study. Patients identification numbers (or subject identifier) are to be given to each patient during the Screening.

9.2. Baseline (Day -1)

Visit on Day -1 is to performed to confirm inclusion/exclusion criteria and collect baseline values for further assessments.

Patients identification is to be followed by alcohol test, urine drugs screen test and urine pregnancy test (for women). Vital signs measurements (respiratory rate, body temperature, 3-positional blood pressure and pulse) are to be performed, followed by 12-lead ECG. Afterwards blood and urine samples for clinical laboratory assessments are to be collected. Baseline assessment of scales is to be performed and the scales are to be performed in order as follows: PANSS, CGI-S, BACS, ESRS, C-SSRS. Afterwards physical, neurological, ophthalmological and dermatological examination are to be performed.

After all the procedures Investigator is to confirm that the inclusion/ exclusion are met. If a patient status after screening changes at Baseline (Day -1) such that the study patient no longer meets all eligibility criteria, then the patient should be excluded from participation in the study (such patient is to be considered as screen failure). It should be remembered that all baseline procedures must be performed on Day -1, but final patient qualification should be made when all results are available, before randomization on Day 0.

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as patient is to be asked to report spontaneously all symptoms and complaint.

9.3. Day 0

On Day 0, the Investigator is to performed the final patient qualification to the study based on all baseline results – this is the case, when not all baseline results (especially laboratory values) are to be available on Day -1.

For a patient meeting all of the inclusion and none of the exclusion criteria the randomization procedure is to be performed.

9.4. Day 1

On Day 1, patient is to receive the first dose of IMP. Before administration (≤ 1h before IMP administration) vital signs measurements are to performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Afterwards blood and urine samples for clinical laboratory assessments, and blood sample for pre-dose PK time point (extensive and sparse group) are to be collected (≤ 1h before IMP administration). With the first PK sampling cannula might be inserted

into a vein shortly prior to the event. If there is cannula occlusion, samples may be obtained via direct venepuncture. IMP is to be administered with hand and mouth check afterwards to ensure the patient have swallowed all capsules. Serial time-points after IMP administration for PK analysis (extensive and sparse group) are to be collected in scheduled time-points (see Section 8.4.1). Within 5 minutes before or after 1h 45 minutes after IMP administration vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Start of ratings is to be within 5 minutes before or after 2h post-dose but after PK blood collection 2h timepoint and the scales are to be performed in order as follows: PANSS, ESRS. Within 5 minutes before or after 9h post-dose vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse).

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on Day -1 (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.5. Days 2 to 6

On Days 2-6, patient is to receive the consecutive doses of IMP. Before administration (≤ 1h before IMP administration) vital signs measurements are to performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Afterwards blood sample for pre-dose PK time point (only extensive group) are to be collected (≤ 1h before IMP administration). IMP is to be administered with hand and mouth check afterwards to ensure the patient have swallowed all capsules. Within 5 minutes before or after 1h 45 minutes after IMP administration vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). PK blood sample are to be collected 2h post-dose for extensive group only. Within 5 minutes before or after 9h post-dose vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse).

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.6. Day 7

On Day7, patient is to receive the consecutive dose of IMP. Before administration (≤ 1h before IMP administration). Vital signs measurements (respiratory rate, body temperature, 3-positional blood pressure and pulse) are to be performed, followed by 12-lead ECG. Afterwards blood and urine samples for clinical laboratory assessments, and blood sample for pre-dose PK time point (extensive and sparse group) are to be collected (≤ 1h before IMP administration). With the first PK sampling cannula might to be inserted into a vein shortly prior to the event. If there is cannula occlusion, samples may be obtained via direct venepuncture. IMP is to be administered with hand and mouth check afterwards to ensure the patient have swallowed all capsules. Serial time-points after IMP administration for PK analysis (extensive group) are to be collected in scheduled time-points (see Section 8.4.1). Within 5 minutes before or after 1h 45 minutes after IMP administration vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Start of ratings is to be within 5 minutes before or after 2h post-dose but after PK blood collection 2h timepoint (extensive and sparse group) and the scales are to be performed in order as follows: PANSS, CGI-S, CGI-I, ESRS. Not earlier than 5h postdose neurological examination is to be performed. Within 5 minutes before or after 9h post-dose vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse).

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.7. Days 8 to 13

On Days 8-13, patient is to receive the consecutive doses of IMP.

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose but starting from 0.5h after IMP administration consumption of low calorie snack i.e. plain rice cakes is allowed till breakfast. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.8. Day 14

On Day 14, patient is to receive the consecutive dose of IMP. Before administration (≤ 1h before IMP administration) vital signs measurements (respiratory rate, body temperature, 3-positional blood pressure and pulse) are to be performed, followed by 12-lead ECG. Afterwards blood and urine samples for clinical laboratory assessments are to be collected (≤ 1h before IMP administration). IMP is to be administered with hand and mouth check afterwards to ensure the patient have swallowed all capsules. Within 5 minutes before or after 1h 45 minutes after IMP administration vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Start of ratings is to be within 5 minutes before or after 2h post-dose and the scales are to be performed in order as follows: PANSS, CG-S, CGI-I, BACS, ESRS, C-SSRS. Not earlier than 5h post-dose neurological examination is to be performed. Within 5 minutes before or after 9h post-dose vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse).

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose but starting from 0.5h after IMP administration consumption of low calorie snack i.e. plain rice cakes is allowed till breakfast. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.9. Days 15 to 20

On Days 15-20, patient is to receive the consecutive doses of IMP.

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose but starting from 0.5h after IMP administration consumption of low calorie snack i.e. plain rice cakes is allowed till breakfast. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.10. Day 21

On Day 21, patient is to receive the consecutive dose of IMP. Before administration (≤ 1h before IMP administration) vital signs measurements (respiratory rate, body temperature, 3-positional blood pressure and pulse) are to be performed, followed by 12-lead ECG. Afterwards blood and urine samples for clinical laboratory assessments are to be collected (≤ 1h before IMP administration). IMP is to be administered with hand and mouth check afterwards to ensure the patient have swallowed all capsules. Within 5 minutes before or after 1h 45 minutes after IMP administration vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Start of ratings is to be within 5 minutes before or after 2h post-dose and the scales are to be performed in order as follows: PANSS, CGI-S, CGI-I, ESRS. Not earlier than 5h post-dose neurological examination is to be performed. Within 5 minutes before or after 9h post-dose vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure pulse).

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose but starting from 0.5h after IMP administration consumption of low calorie snack i.e. plain rice cakes is allowed till breakfast. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration).

9.11. Days 22 to 27

On Days 22-27, patient is to receive the consecutive doses of IMP.

Requests for AEs and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose but starting from 0.5h after IMP administration consumption of low calorie snack i.e. plain rice cakes is allowed till breakfast. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration.

9.12. Day 28

On Day 28, patient is to receive the last dose of IMP. Before administration (≤ 1h before IMP administration) vital signs measurements (respiratory rate, body temperature, 3-positional blood pressure and pulse) are to be performed, followed by 12-lead ECG. Afterwards blood and urine samples for clinical laboratory assessments, and blood sample for pre-dose PK time point (extensive and sparse group) are to be collected (≤ 1h before IMP administration). With the first blood sampling cannula might to be inserted into a vein shortly prior to the event. If there is cannula occlusion, samples may be obtained via direct venepuncture. IMP is to be administered with hand and mouth check afterwards to ensure the patient have swallowed all capsules. Within 5 minutes before or after 1h 45 minutes after IMP administration vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse). Start of ratings is to be within 5 minutes before or after 2h post-dose but after PK blood collection 2h timepoint (extensive and sparse group) and the scales are to be performed in order as follows: PANSS, CGI-S, CGI-I, BACS, ESRS, C-SSRS. Not earlier than 5h post-dose physical, neurological, ophthalmological and dermatological examination are to be performed. Within 5 minutes before or after 9h post-dose vital signs measurements are to be performed (respiratory rate, body temperature, 3-positional blood pressure and pulse).

Requests for AE and information about the concomitant medications if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

Patient is to fast from supper on day before (fasting at least 10 hours prior to dosing) with continued fasting for 2 hours post-dose. Water and other fluids are to be restricted one hour before and one hour after dosing (excluding amount of water allowed for IMP administration.

9.13. Day 29

Starting from Day 29 there are no IMP administration. On Day 29, the patient may resume antipsychotic treatment. Urine pregnancy test is to performed for women patients. Requests for AE and information about the concomitant medications, if any, are to be performed by the

Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

At the Investigator discretion 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).

9.14. Follow-up visits

To follow-up on study patient visits 7 days (± 1 day) and 14 days (± 1 day) post-last dose are to be performed.

After arrival at the clinic patient identification is to be followed by alcohol test, urine drug screen and urine pregnancy test (for women). Vital signs measurements (respiratory rate, body temperature, 3-positional blood pressure and pulse) are to be performed, followed by 12-lead ECG. Afterwards blood and urine samples for clinical laboratory assessments are to be collected. Rating using ESRS and C-SSRS scales and also physical and neurological examinations are to be performed.

Requests for AE and information about the concomitant medications, if any, are to be performed by the Investigator to each patient during the study as well as subject is to be asked to report spontaneously all symptoms and complaints.

10. STATISTICAL CONSIDERATIONS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the clinical study report (CSR).

10.1. Study Population

10.1.1. Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented by treatment.

10.1.2. Protocol Deviations

Protocol deviations will be listed by subject.

10.1.3. Analysis population

- 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 Set (SS): All patients who received at least 1 dose of study treatment (either CPL500036 or placebo).
- Pharmacokinetic Set (PS): All subjects in the safety set with at least 1 evaluable PK parameter.
- Pharmacokinetic Set for parameter calculation (PSPC): All subjects 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.

10.2. Evaluation of Efficacy

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis for the respective treatment group. For continuous variables, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. For all analyses data from all centres will be pooled.

10.3. Primary Efficacy Analysis

The null hypothesis is that there is no difference in the primary endpoint between either dose group compared to placebo, versus the alternative hypothesis, that at least 1 dose group is significantly different, using a 2-sided 10% significance level. The primary endpoint will be analysed using a mixed effect repeated measures model (MRMM), with treatment, timepoint, clinical site and interaction between treatment and timepoint as fixed effects and baseline score as a covariate. If there will be many clinical sites with few subjects, they can be pooled into bigger groups. 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. A sensitivity analysis will be conducted whereby missing data is imputed using multiple imputation. The primary analysis will compare each dose group with placebo based on estimated marginal means (aka least square means, LS-means) from the model.

10.4. Secondary Efficacy Analyses

All secondary endpoints will be analysed without adjustment for multiplicity. The secondary endpoints, which are continuous, will be analysed using the same approach as described for the primary endpoint. 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) will be analysed at each timepoint using a Logistic regression model with treatment and clinical site (or country if there will be many clinical sites) as a fixed effect and baseline score as a covariate. In sensitivity analysis, if a patient is missing data in order to derive their response at a given time point, the missing data will be imputed using multiple imputation for continuous endpoints and non-responder imputation for binary endpoints prior to the analysis.

10.5. General Considerations

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, SD, minimum, median and maximum). Categorical data will be summarized by treatment group using frequency tables (number and percentage).

10.6. Protocol Deviations

All protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with the CRO SOPs.

10.7. Subject Disposition

Subjects excluded from the safety, PK and PD analysis sets and data excluded from the PK and PD analysis sets will be listed including the reason for exclusion. Subject disposition will be summarized and will include the following information: number of subjects randomized and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomized.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

A randomization listing will be presented and include the following: each subject's/patient's randomization number, the subject's/patient's full enrolment number, the treatment to which the subject/patient has been randomized and the location of the Clinical Unit.

10.8. Demographic and Anthropometric Information and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight and BMI) will be listed by subject. Demographic characteristics (age, sex, ethnicity and race) and anthropometric characteristics (height, weight and BMI) will be summarized by treatment and for all subjects in the FAS, SS, PP and PSPC populations. The denominator for percentages will be the number of subjects in the given analysis set for each treatment or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA SOC, MedDRA preferred term, start date, and stop date (or ongoing if applicable), as well as summarized by treatment group and overall for full analysis set.

10.9. Prior and Concomitant Medication and Drug Administration

Prior medications are those that started and stopped prior to the first dose of IMP. Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be classified using the ATC codes contained in Register of Medicinal Products Approved for Marketing on the territory of the Republic of Poland and listed by subject and will include the following information: reported name, preferred term, ATC level 2 (therapeutic subgroup) and 4 (chemical subgroup), the route of administration, dose, frequency, start date/time, duration and indication. Summary of prior and concomitant medications will be provided as a count and frequency for ATC level 2 and 4.

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Drug administration dates and times will be listed for each subject.

10.10. Exposure

A listing of drug administration will be created and will include the date and time of administration. When appropriate, a summary table of compliance will also be created.

10.11. Safety Analyses

10.11.1. Adverse Events

All AEs will be listed. The number and percent of subjects experiencing an event will be tabulated for each SOC and preferred term. The AEs will also be tabulated according to intensity and causality. An overview table presenting the incidence of AE will be presented. All tables will be prepared separately by number of patients and number of events.

Serious AEs will be listed separately.

10.11.2. Clinical Laboratory Tests

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.

Clinical laboratory tests (observed values) as well as change from baseline and categorization of results will be summarized descriptively in tabular format. Shift tables will be presented for selected laboratory parameters.

10.11.3. Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital signs findings that were considered AEs by the Investigator will be presented in the AE listings.

Observed values as well as change from baseline will be summarized descriptively in tabular format.

10.11.4. Standard 12-lead Electrocardiogram

Standard 12-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values will be summarized descriptively in tabular format. Change from baseline will be summarized descriptively for all parameters. A categorical analysis will also be performed as well as shift tables.

10.11.5. Physical Examination

Abnormal physical examination findings will be listed.

10.11.6. Other Safety Variables

Abnormal neurological, ophthalmological and dermatological examinations findings will be listed.

Descriptive statistics of the score and change from baseline will be summarized at each scheduled time point for extrapyramidal side effects - ESRS scale.

10.12. Pharmacokinetics Analyses

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 separate using descriptive statistics. Additional analysis, if deemed appropriate, will be described in the SAP.

A population pharmacokinetic model may be developed. If so, the analysis plan and the results would not be included in the CSR but in separate documents.

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.

10.13. Pharmacokinetics/Pharmacodynamics Analyses

An exploratory PK/PD analysis between the AUC_{0-24} and C_{max} of CPL500036 and the 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.

10.14. Interim Analyses

No formal interim analysis is planned.

10.15. Timing of analysis

Baseline characteristics 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.

10.16. Determination of 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).

11. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

11.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, Celon Pharma S.A. or its representative will ensure the following:

- development and provision of instructional material to the study sites, as appropriate;
- start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures as well as IMP handling and management;
- periodic monitoring visits to the study site by blinded and unblinded Clinical Research Associates;
- availability for consultation and regular contact with the study site personnel by mail, telephone;
- revision and evaluation of CRF data and use standard computer edits to detect errors in data collection;
- quality review of the database.

Celon Pharma S.A. or its representative will periodically check a sample of the patient data recorded against source documents at the study site during monitoring visits.

The study may be also audited by Celon Pharma S.A. or designee, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to Good Clinical Practice (GCP) and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator.

Protocol deviations will be handled in accordance with the CRO SOPs.

11.2. Data collection and Access to Source Data/Documents

Celon Pharma S.A. will use an electronic data capture (EDC) system to completely collect all medical data during this study. Electronic data capture system is a software tool designed similarly to an electronic medical record for the documentation of e.g., medical history, demographics, vital signs, and AEs.

The Investigator will ensure the accuracy, completeness and timeliness of the data reported to the Sponsor. System supported data collection processes and procedures are validated to ensure completeness, accuracy, reliability and consistency. A complete audit trail is maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks (plausibility and completeness) will be used along with the Investigator review to identify any errors or inconsistencies in the data. Data clarification requests will be provided to the study team by means of electronic or manual queries.

During the study setup, adequate and accurate clinical procedure forms are used to generate medical records, digital ECGs, AE and concomitant medication reporting, raw data collection forms, etc., which are designed as protocol to record all observations and other pertinent data for each subject receiving study medication. The only regularly used paper-based study document is the ICF, because it requires wet-ink signatures. The ICFs will be archived in paper form at the end of the study.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IEC to have direct access to all electronic records pertaining to the study.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.3. Archiving Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures.

The Investigator's Site File will be archived by the Clinical Centre for 15 years after completion of the study. The Trial Master File will be archived by the Sponsor for 15 years after completion of the study.

11.4. Good Clinical Practice

The procedures set out in this CSP are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP. The clinical study also will be carried out in keeping with national and local legal requirements

11.5. Informed Consent

Eligible subjects may only be included in the study after providing IRB/IEC approved informed consent.

Informed consent must be obtained from the subject before conducting any study-specific procedure.

As part of the informed consent procedure, the Investigator must explain orally and in writing the nature, duration and purpose of the study and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences or AEs that may occur. The subject should be informed that he/she is free to withdraw from the study at any time. Subjects will receive all information that is required by local regulations and ICH guidelines. The ICF must be signed and dated; 1 copy will be handed to the subject, and the Investigator will retain a copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must be documented in the subject source documents.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all subjects subsequently enrolled in the clinical study, as well as those currently enrolled in the clinical study as applicable.

11.6. Insurance and Compensation for Injury

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator’s Site File.

11.7. Protocol Approval and Amendment(s)

Before the start of the clinical study, the CSP and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff and receive IRB/IEC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated CSR. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

11.8. Confidentiality Data Protection

The CRO and the Sponsor will take appropriate measures to ensure the processing of personal data and the free movement of such data are handled according to the European Union General Data Protection Regulation 2016/679.

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name, or by subject number and birth year only, if required and to comply with local data protection regulations. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Investigator.

11.9. Publication Policy

By signing the CSP, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the regulatory authorities will be notified of the Investigator’s name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

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13. APPENDICES

Appendix No.1 *Table 9. Drugs Allowed (Y) and Not Allowed (N) as Concomitant Medications.*

Appendix No. 2 *Investigator Signature Page Template.*

Table 9. Drugs Allowed (Y) and Not Allowed (N) as Concomitant Medications

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
Akathisia management	Y	N	Only episodic propranolol administration is allowed, detailes on dosage and restrictions outlined in Section 5.4.3, Table 5,
Analgesics	Y	Y	Nonnarcotic analgesics are allowed. Tramadol and indomethacin are not allowed. Pregabalin, gabapentin and other gabapentinoids are not allowed. Medically appropriate episodic use of narcotic analgesics for acute medical indications limited to 3 days for an episode is allowed, except on days of efficacy evaluations.
Anesthetics, general	Y	N/A	If procedures requiring general anesthesia are to occur/have occurred, please contact the Forest Medical Monitor to report the medical condition(s).
Anesthetics, local	Y	N	-
Antacids	Y	Y	Not within 8h before and 4h after IMP administration.
Anti-acne	Y	Y	Topical agents only, including topical antibiotics.
Antianginal agents	N	N	-
Antiarrhythmics	N	Y	Dosages should be stable for 1 month before Visit 1 (Screening). For patients on digoxin, there should be a digoxin level obtained within 2 months before Screening.
Anti-asthma agents	Y	Y	Systemic corticosteroids are not allowed.

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
			Inhaled steroids at approved dosages are allowed.
Antibiotics	Y	N	Chronic use of topical antibiotics for acne is allowed. Linezolid (Zyvox) and isoniazid are not allowed. Erythromycin, clarithromycin, telithromycin, chloramphenicol, rifampicin and rifabutin are not allowed. Azithromycin is recommended if a macrolide antibiotic is needed.
Anticholinergics in extrapyramidal symptoms management	Y	N	Only episodic benzatropine/biperiden administration is allowed, detailes on dosage and restrictions outlined in Section 5.4.3, Table 5,
Anticoagulants	N	N	Warfarin (Coumadin) use is not allowed. Some antiplatelet agents are allowed (see below).
Anticonvulsants	N	N	-
Antidepressants	N	N	-
Antidiarrheal preparations	Y	N	Only loperamide HCl (Imodium), bismuth subsalicylate (Pepto-Bismol), and kaolin preparations are allowed.
Antiemetics	Y	N	Antidopaminergic agents (such as metoclopramide, domperidone and phenothiazines), scopolamine, 5-HT3 receptor antagonists (e.g., ondansetron) and sedating (H1) antihistamines are not allowed. Phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto-Bismol), and cola syrup are allowed.

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
Antifungals, systemic	N	N	-
Antifungals, topical	Y	Y	-
Anti-gout medications	Y	Y	Probenicid is not allowed.
Antihistamines	Y	Y	Sedating antihistamines are not allowed. Only fexofenadine (Allegra), loratadine (Claritin), desloratadine (Clarinex), cetirizine (Zyrtec) and levcetirizine (Xyzal) are allowed for episodic or chronic use. Terfenadine is not allowed. See Cough and Cold Preparations for combination products.
Antihypertensives	N	Y	Reserpine (Diupres), clonidine (Catapres), guanabenz (Wytensin), guanfacine (Tenex and Intuniv), guanethidine (Ismelin), methyldopa (Aldomet), direct vasodilators (hydralazine, minoxidil), nitroglycerin, sodium nitroprusside, and diazoxide are not allowed. Propranolol (Inderal) is not allowed. For all others (α1-blockers, β-blockers, calcium channel blockers, ACE inhibitors, etc), the medication and dosage should be stable for 1 month before Screening (for diuretics, the patient should have been treated with the diuretic for at least 3 months, with at least 1 month on the current dose).
Anti-inflammatory drugs	Y	Y	Chronic use is allowed if dosage is stable for 1 month prior to Screening. Indomethacin (Indocin) and systemic

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
			corticosteroids are not allowed.
Antimigraine	Y	N	Ergotamine or ergot derivatives are not allowed. Narcotics, antidepressants, and anticonvulsants are not allowed.
Antinauseants	Y	N	Only phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto-Bismol), and cola syrup are allowed. 5-HT3 receptor antagonists (e.g. ondansetron), sedating (H1) antihistamines, and prokinetic agents (metoclopramide) are not allowed.
Antineoplastics	N	N	-
Antiobesity/Appetite suppressants	N	N	-
Antiplatelet agents	N	Y	Only Aspirin (maximum 325 mg/d) and clopidogrel (Plavix) are allowed. Ticlopidine is not allowed. Medication dosage must be stable for 1 month prior to Screening.
Antipsoriatic treatments	Y	Y	Acitretin (Soriatane) is not allowed.
Antipsychotics	N	N	-
Antismoking medications	Y	Y	Only nicotine replacement therapy patches are allowed.
Antiviral agents	Y	Y	Only oral or topical agents are allowed. Only acyclovir, famciclovir, valacyclovir, penciclovir, docosanal, trifluridine, and vidarabine are allowed. Amantadine and rimantadine are permitted for influenza prophylaxis but use is limited to a 7- to 14-day course. Interferons are not allowed. Anti-HIV drugs are not allowed.

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
Anxiolytics	Y	N	Only episodic lorazepam administration is allowed, detailes on dosage and restrictions outlined in Section 5.4.3, Table 5,
Cough and /Cold preparations	Y	N	Cough/cold preparations containing dextromethorphan or narcotics are not allowed. Decongestant preparations containing pseudoephedrine or phenylpropanolamine are **not** allowed. Phenylephrine nasal sprays are allowed for brief medically appropriate use, for up to 5 days. Combination products containing the word "Nighttime" or some synonym routinely include a sedating antihistamine and are not allowed. Combination products ending in "D" routinely contain a stimulant such as pseudoephedrine or phenylpropanolamine and are **not** allowed (also see Antihistamines).
Diuretics	Y	Y	For chronic use, medication and dosage should be stable for 1 month before Screening (note, as a antihypertensive, diuretics should have been prescribed for at least 3 months, with at least 1 month on the current dose).
Gastrointestinal: H2-blockers/ proton pump inhibitors/ prokinetic agents	Y	Y	Cimetidine (Tagamet) is not allowed. Metoclopramide is not allowed.
Hormonal (noncontraceptive)	N	Y	-

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
therapies			
Hormone suppressants	N	Y	Only finasteride (Proscar) and dutasteride (Avodart) are allowed. Dosage must be stable for 3 months prior to Screening
Hormones: reproductive	N	Y	Hormonal contraception such as oral contraceptives (estrogen-progestin combination or progestin alone), transdermally delivered contraceptives (e.g., Ortho Evra), depot injections (e.g., Depo-Provera), vaginal contraceptive ring (e.g., NuvaRing) and contraceptive implant (e.g., Implanon, Norplant) are allowed.
Hormones: thyroid	N	Y	Thyroid hormone replacement is allowed (dosage of thyroid medication should be stable for 2 months before Screening). Therapeutic use for psychiatric disorders (e.g., T3 antidepressant augmentation) is not allowed
Hypoglycemic agents	N	Y	Oral hypoglycemic agents are allowed, except pioglitazone and troglitaxone are not allowed. Insulin is not allowed.
Hypolipidemics: bile acid sequestrants; fibrates; niacin; statins	N	Y	*Niacin and niacinamide are allowed if the dose has been stable for 3 months prior to Screening, and AST and ALT are ≤ 1.5 times the upper limit of normal. Ezetimibe (Zetia) is allowed. Gemfibrozil and fenofibrate are allowed. Statins (e.g., Lovastatin,

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
			simvastatin, pravastatin, atorvastatin, fluvastatin, and rosuvastatin) are allowed. Dosage must be stable for 1 month prior to Screening. Bile sequestrants are not allowed. Call the Medical Monitor to discuss combinations.
Insulin	N	N	-
Laxatives	Y	Y	Episodic and chronic use of bulk laxatives and emollient laxatives are allowed. Episodic use of stimulant laxatives containing senna, bisacodyl, and anthraquinone derivatives is allowed. Episodic use of osmotic laxatives such as oral magnesium hydroxide (milk of magnesia), oral sodium citrate and sodium biphosphate is allowed. Hyperosmotic laxatives such as sorbitol, lactulose, and polyethylene glycol are not allowed.
Lithium	N	N	-
Muscle relaxants	N	N	Soma, Flexeril, Skelaxin, etc. are not allowed.
Psychotropic drugs not otherwise specified (including herbal products)	N	N	No drugs with psychomotor effects or with anxiolytic, antidepressant, stimulant, antipsychotic, mood stabilizers or sedative properties are allowed except as stipulated by the protocol. Herbal/dietary products and supplements with potential psychoactive actions, including St. John's wort, Ginkgo biloba, kava kava, SAMe, valerian root, DHEA, tyrosine,

Drugs name or Class	Episodic Use (PRN)	Chronic Use	Restrictions
			tryptophan 5-HTP and melatonin are not allowed. Omega-3 supplements are not allowed..
Sedatives/Hypnotics	Y	N	Only episodic lorazepam and zolpidem administration is allowed, details on dosage and restrictions outlined in Section 5.4.3, Table 5, Other benzodiazepines and z-drugs are not allowed.
Steroids, systemic	N	N	-
Steroids, local	Y	Y	-
Stimulants/ADHD medications	N	N	Oral or transdermal methylphenidate, amphetamine products or prodrugs, pemoline (Cylert), pseudoephedrine, modafinil (Provigil), and armodafinil (Nuvigil) are not allowed. Clonidine (Catapres), guanfacine (Tenex) and guanfacine extended-release (Intuniv) are not allowed.
Vaccines	Y	N/A	-

PRN = as needed

SIGNATURE PAGE

Declaration of the Investigator

I have read and understood the protocol version 4.0, dated 16th May 2024, specified below, and agree on the contents.

Protocol Title: 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.

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice applicable to this clinical study.

I have read all pages of this clinical study protocol, version 4.0, dated 16th May 2024 and confirm that it contains all the information required to conduct this study. I agree to conduct the study as detailed in the protocol and comply with all the terms and conditions set out therein. I confirm that I is to conduct the study in accordance with the provisions of the Declaration of Helsinki. I will also ensure that Investigator(s) and other relevant members of my staff have access to copies of this protocol and the Declaration of Helsinki to enable them to work in accordance with the provisions of the documents and standard operating procedures of designated CRO company. Furthermore, current ICH-GCP, and local regulations is to be followed.

I acknowledge that all data included in the clinical study protocol are confidential. Copying, disclosing and publishing without assent of Sponsor is prohibited.

Investigator Signatory

Signature	Date

Name	
Title	
Institution	