SEP-363856

Clinical Study Protocol SEP361-201

A 4-Week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexibly-dosed, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adult Subjects With Schizophrenia

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician		Telephone: Email:
Medical Monitor		Office: Mobile: Email:
SAE/Pregnancy Reporting		Hotline Number: Fax: Email:

1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals, Inc.

Name of Investigational Product: SEP-363856

Title of Study: A 4-Week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexibly-dosed, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adult Subjects With Schizophrenia

Proposed Indication: Schizophrenia

Study Centers: Approximately 35 centers globally

Phase of Development: 2

Study Objectives:

Primary: To evaluate the efficacy of flexibly dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS).

Secondary:

- To evaluate the efficacy of flexibly-dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by:
  - Clinical Global Impression-Severity (CGI-S)
  - PANSS subscale scores (positive, negative, and general psychopathology)
  - Brief Negative Symptom Scale (BNSS)
  - Montgomery-Asberg Depression Rating Scale (MADRS)
- To evaluate the safety and tolerability of SEP-363856 (50 or 75 mg/day) using
  - physical examinations (PE)
  - 12-lead electrocardiograms (ECG)
  - vital signs
  - adverse event (AE) reports
  - clinical laboratory results
  - body weight and body mass index (BMI)
  - Columbia – Suicide Severity Rating Scale (C-SSRS)

Other:

- To assess whether SEP-363856 is associated with extrapyramidal symptoms as measured by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS).
- To characterize the effects of SEP-363856 as measured by the Drug Effects Questionnaire (DEQ).
- To characterize the subjective effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI).
- To assess the effects of SEP-363856 on cognition based on the CogState Brief Battery (CBB).

- To perform population pharmacokinetic (POPPK) analysis using plasma SEP-363856 concentrations
- To explore the relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods.
- To explore the impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on SEP-363856 plasma exposure.

Study Design:

This is a multicenter, randomized, double-blind, parallel-group, flexibly-dosed, study evaluating the efficacy and safety of SEP-363856 in acutely psychotic adult subjects with schizophrenia using SEP-363856 (50 or 75 mg/day [ie, once daily]) versus placebo over a 4-week treatment period. This study is projected to randomize at least 240 subjects to 2 treatment groups (SEP-363856 or placebo) in a 1:1 ratio. The treatment assignment will be balanced within each clinical site. Subjects randomized to placebo will receive placebo treatment throughout the study. Study drug will be taken at the same time each evening before bed time and may be taken with or without food.

The study will consist of 3 periods: Screening/Washout (up to 14 days), Treatment (4 weeks in-patient), and a Follow-up visit (7 days after last study drug dose for subjects who discontinue prior to Visit 7 or who complete the study but do not elect to enroll in the open-label extension study [SEP361-202]) as shown in Figure 1.

Screening/Washout Period (up to 14 days):

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days, during which they will be tapered off all psychotropic medications (except as noted in the protocol) in a manner that is consistent with labeling recommendations and conventional medical practice. Subjects will remain hospitalized for the duration of the screening/washout period.

Double-Blind Treatment Period (4 weeks):

During the double-blind phase, subjects will be in-patient through Week 4. Subjects will be eligible for hospital discharge after the Week 4 visit (Day 29).

Randomization/Treatment: At double-blind Baseline (Day 1), subjects who have successfully completed the washout of prior medication (see Section 10.3.1) and have met the randomization criteria (see below) will be randomly assigned via interactive web/voice response system (in a 1:1 ratio) to one of two treatment arms: SEP-363856 or placebo. Study drug dosing will initiate the evening of the Baseline visit. Treatment will continue once-daily at night for the remainder of study during which procedures outlined in Table 2 will be conducted.

Subjects will receive SEP-363856 50 mg/day on Day 1 through 3. On Day 4, subjects are permitted (but not required) to titrate up to a dose of 75 mg/day. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits/weekly intervals starting from Visit 4 based on Investigator judgement. A dose reduction for tolerability purposes is permitted to occur more frequently than at weekly intervals. Subject can be flexibly dosed up until Visit 6, but no dose adjustments are allowed thereafter.

End of Double-Blind Period:

Subjects who complete the 4-week double-blind treatment phase will be eligible to participate in a separate open-label 26-week extension study (Study SEP361-202). Subjects who discontinue early from the study or complete the study and do not enter the 6-month extension study will be required to complete the follow-up visit 7 days (± 2 days) post last dose of study drug.

Upon completion or early discontinuation from the study, hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary. Prior authorization for the hospitalization must be approved by the Medical Monitor. After completion of the follow-up visit or upon study discontinuation, all subjects will be referred for appropriate continued treatment and follow-up care as determined by the Investigator.

Efficacy, Safety, and Pharmacokinetic Evaluations

Efficacy will be evaluated using the PANSS total and subscale scores, as well as CGI-S, BNSS, and MADRS scores. Effect of SEP-363856 on cognition will be assessed by the CBB.

Safety and tolerability will be monitored throughout the study by collection of physical examination (PE) results, ECGs, vital signs, AEs, clinical laboratory parameters, C-SSRS, body weight, and BMI. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation.

Subjects will provide information on subjective drug effects via administration of the DEQ. In addition, effects on movement disorders will be measured using the AIMS, BARS and SAS scales. Subjective effects on sleep will be measured by the PSQI scale.

Blood samples for plasma SEP-363856 and SEP-363854 concentrations will be collected on Day 1 (predose) and Day 29. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods exposure will be explored and reported separately. The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on plasma SEP-363856 exposure will be explored and reported separately.

Diagnosis and Main Criteria for Subject Inclusion:

See Section 8 of full protocol for the complete list of inclusion and exclusion criteria information.

Inclusion criteria (not all inclusive):

To qualify for participation, subjects must meet all of the following inclusion criteria:

1. Male or female subject between 18 to 40 years of age (inclusive) at the time of consent.
2. Subject meets DSM-5 criteria for schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the SCID-CT). The duration of the subject's illness whether treated or untreated must be ≥ 6 months.
3. Subject must have a CGI-S score ≥ 4 (moderate or greater) at screening and Baseline (Day 1).
4. Subject must have a PANSS total score ≥ 80 and a PANSS item score ≥ 4 (moderate) on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at screening and Baseline (Day 1).
5. Subject has an acute exacerbation of psychotic symptoms (no longer than 2 months).
   - Subject has marked deterioration of functioning in one or more areas, such as occupational, social, or personal care or hygiene.
   - Subject requires hospitalization for an acute psychotic exacerbation at the time of screening or has been hospitalized for the purpose of treating an acute psychotic exacerbation for no more than 2 consecutive weeks immediately before screening.

     Subjects who have been hospitalized for more than 2 weeks for reasons unrelated to acute psychotic exacerbation may be included if such a hospitalization was for a condition other than an acute psychotic relapse. For example, subjects in a long-term hospital setting who have an acute exacerbation and are transferred to an acute unit are eligible for the study.
6. Subject has had no more than 2 prior hospitalizations for the treatment of an acute exacerbation

of schizophrenia (not including the current hospitalization). This history must be confirmed based on report by a reliable informant (eg. caregiver or family member) or medical records available at the time of screening.

7. At Baseline, subject must have a total score < 5 on the SAS.

Exclusion Criteria (not all inclusive):

To qualify for participation, subjects must not meet any of the following exclusion criteria:

1. Subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at or during the Screening period (ie, in the past one month) and/or at Baseline (ie, since last visit).
2. Subject has previously received SEP-363856.
3. Subject has a lifelong history or presence of symptoms consistent with a major psychiatric disorder other than schizophrenia as defined by DSM-5. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months), substance (other than nicotine or caffeine) use disorder within past 12 months, major depressive disorder, bipolar depression, mania, schizoaffective disorder, obsessive compulsive disorder, posttraumatic stress disorder. Previous or current symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms have not been a focus of primary treatment.
4. Subject is at significant risk of harming self, others, or objects based on Investigator's judgment.
5. Subject has attempted suicide within 3 months prior to screening.
6. Subject is involuntarily hospitalized.
7. Subject is receiving a total dose of antipsychotic medication equivalent to≥ 12.0 mg/day of haloperidol at Screening (see Section 22, Appendix III for table of haloperidol dose equivalents). Subject may be eligible if such treatment is less than 2 weeks in duration after consultation with the Medical Monitor.
8. Subject has received electroconvulsive therapy treatment within the 6 months prior to screening or is expected to require ECT during the study.
9. Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents, given at adequate dose for at least 4 weeks within a 1 year period prior to Screening.
10. Subject has a history of treatment with clozapine for refractory psychosis and/or subject has been treated with clozapine (for any reason) within 4 months of Screening.
11. Subject is currently participating, or has participated in, a study with an investigational or marketed compound or device within 6 months prior to signing the informed consent, or has participated in 2 or more studies within 24 months prior to signing informed consent.

Randomization Criteria

To qualify for randomization, subjects must meet all of the following randomization criteria:

1. Subject must have a PANSS total score ≥ 80 at Baseline (Day 1).
2. Subject must have a PANSS item score ≥ 4 on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at Baseline (Day 1).

3. Subject must not demonstrate a decrease (improvement) of ≥ 20% in the PANSS total score between Screening and Baseline visits (see Section 26, Appendix VII for calculation of PANSS total score improvement) , or the PANSS total score falls below 80 at Baseline (Day 1).
4. Subject must have a CGI-S score ≥ 4 at Baseline (Day 1).
5. Subject must have a total score < 5 on the SAS at Baseline (Day 1).
6. Subject must not answer "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Baseline (ie, since last visit).
7. Subject must meet all other inclusion and none of the exclusion criteria at Baseline (Day 1).

Investigational Product, Dosage and Mode of Administration:

SEP-363856 treatment will be size 0, Swedish-orange capsules (50 mg or 75 mg) administered orally once daily. Study drug will be taken at the same time each evening before bed time and may be taken with or without food.

Subjects will receive SEP-363856 50 mg/day on Day 1 through 3. On Day 4, subjects are permitted (but not required) to titrate up to a dose of 75 mg/day. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits/weekly intervals starting from Visit 4 based on Investigator judgement. A dose reduction for tolerability purposes is permitted to occur more frequently than at weekly intervals. Subject can be flexibly dosed up until Visit 6, with no dose adjustments allowed thereafter.

Duration of Treatment: 4 weeks

Reference Therapy, Dosage and Mode of Administration:

Matching placebo treatment will be size 0, Swedish-orange capsules administered orally once daily. Study drug will be taken at the same time each evening before bed time and may be taken with or without food.

Subjects randomized to placebo will receive placebo throughout the study.

Concomitant Medications:

Concomitant Non-psychotropic Medications:

Medications for short-term treatment of an acute medical condition are allowed after consultation with the Medical Monitor. Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after randomization if the dose and regimen have been stable (± 25%) for at least 30 days prior to screening. The dose for the concomitant medication may change, as needed, after randomization (or be discontinued). β-adrenergic antagonists used to treat stable hypertension may be continued through the screening phase and post-randomization. In addition, use of over-the-counter non-prescription pain medications (eg, aspirin, acetaminophen) are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study drug. Female subjects may use oral, patch, or IUD hormonal contraceptives, or progestin implant or injection (detailed information on allowed contraceptives is defined in Section 21 of the full protocol).

Prior Medications:

Prior treatment with antipsychotic agents must be discontinued in a manner consistent with general medical practice during the screening period for at least 3 days. Depot neuroleptics must be discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to the screening visit.

Prior treatment with antidepressants must be discontinued as tolerated and clinically appropriate as follows:

- MAO inhibitors – at least 14 days prior to baseline (Day 1)
- Fluoxetine hydrochloride – at least 28 days prior to baseline (Day 1)
- Clozapine – at least 120 days prior to screening

Prior treatment with mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine, etc.) must be discontinued as tolerated and clinically appropriate at least 7 days prior to double-blind Baseline. All other psychotropic medication (except as described in this section), including antipsychotic medication, must be discontinued, as tolerated and clinically appropriate, prior to randomization in a manner that is consistent with labeling recommendations and conventional medical practice.

Concomitant Psychotropic Medications:

All antidepressants and mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine, etc.) are not allowed during the study. Treatment with benztropine (benzotropine outside the United States [US]) up to 6 mg/day will be permitted, as needed, for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with propranolol (up to 120 mg/day) will be permitted as needed for akathisia.

Medications used to treat movement disorders should not be given prophylactically.

Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem and zolpidem CR is permitted at the discretion of the Investigator with the following restrictions:

- lorazepam (or equivalent benzodiazepine) is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular lorazepam is permitted up to 4 mg/day for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per investigator judgment.
- temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day for males; ≤ 5 mg/day for females), and zolpidem CR (≤ 12.5 mg/day for males; ≤ 6.25 mg/day for females) may be administered at bedtime for insomnia, as needed.
- hypnotic agents should be administered no more than once nightly and should not be used in combination.

The date and time of the last dose taken prior to scheduled efficacy assessments must be recorded at each visit. Subjects should be encouraged to avoid taking these concomitant medications within 8 hours of scheduled efficacy assessments.

Opioids may be allowed for a limited period of time with prior authorization from the Medical Monitor.

See Section 10.3 of full protocol for the complete list of concomitant medications and restrictions.

Study Endpoints:

Primary Endpoint:

- Change from Baseline in PANSS total score at Week 4.

Secondary Endpoints:

- Change from Baseline in CGI-S score at Week 4.
- Change from Baseline in PANSS subscale scores at Week 4.

- Change from Baseline in BNSS total score at Week 4
- Change from Baseline in MADRS total score at Week 4.
- Proportion of subjects who achieve a response, defined as a 20% or greater improvement from Baseline in PANSS total score at Week 4.
- The incidence of overall AEs, serious AEs (SAEs) and AEs (or SAEs) leading to discontinuation.
- Absolute values and changes from Baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], 12-lead ECGs).
- Frequency of subjects with suicidal ideation or suicidal behavior using the C-SSRS.

Other Endpoints:

- Change from Baseline in BARS, AIMS and SAS scores at Week 4.
- Absolute visual analogue scale (VAS) scores of the DEQ.
- Change from Baseline in PSQI score at Week 4.
- Change from Baseline in CBB total score at Week 4.

Statistical Methods:

The analysis of efficacy will be based on the modified Intent-to-Treat (mITT) population, which includes all subjects who are randomized, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline efficacy measurement in PANSS or CGI-S. The safety assessments will use the Safety population, which includes all subjects who are randomized and have received at least one dose of study drug.

The primary efficacy variable is the change from Baseline in PANSS total score at Week 4 for testing superiority of SEP-363856 compared to placebo. The primary efficacy variable will be analyzed using a Mixed Model for Repeated Measures (MMRM). The MMRM model will include factors for treatment, visit (Day 4, Weeks 1, 2, 3, and 4; as a categorical variable), pooled center, and treatment-by-visit interaction, and include Baseline PANSS total score as a covariate. An unstructured covariance matrix will be used for the within-subject correlation and the Kenward-Rogers approximation will be used to calculate the denominator degree of freedom.

Sensitivity analyses will be conducted to assess the robustness of the MMRM analysis result of the primary endpoint. The methods will include the random effects pattern-mixture model and the pattern-mixture model with placebo-based multiple imputation.

The secondary efficacy variables of change from Baseline at Week 4 in CGI-S score, PANSS subscale scores, BNSS total score, and MADRS total score will be analyzed similarly to the primary variable.

The subjects who achieve a response are defined as subjects having a 20% or greater improvement in PANSS total score from Baseline at the last observation carried forward (LOCF) endpoint. A logistic regression will be performed with the responder indicator as the dependent variable, and include treatment and geographic region as fixed factors, and Baseline PANSS total score as a covariate.

Safety data including AEs, laboratory values, clinical evaluations, and C-SSRS, will be summarized.

Adverse events, AEs leading to discontinuation, and serious AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects with any AEs, and AEs by system organ class and preferred term. Adverse events will be further summarized by severity and by relationship to study drug. The summary of AEs will include any AE occurring on or after the first dose of study drug.

A nonparametric rank analysis of covariance (ANCOVA) will be applied to prolactin, HbA_{1c}, lipids, and glucose levels, as well as body weight and BMI in order to compare changes from Baseline

between treatment groups with adjustments for Baseline value.

Sample Size:

A sample size of 100 subjects per treatment group (SEP-363856 and placebo) will provide 80% power to detect a treatment effect size of 0.4 in change from Baseline in PANSS total score at Week 4 for SEP-363856 versus placebo, using a two independent sample t-test method with 2-sided significant level of 0.05. A clinically meaningful effect size of 0.4 was estimated based on review of published studies of other antipsychotics for the short-term treatment of schizophrenia. It is anticipated that 17% of all randomized subjects will discontinue early from the study. An upward adjustment of the sample size is thus used to compensate for missing data from subjects who are randomized and discontinue from the study. The total sample size will be 240 randomized subjects (or 120 subjects per treatment group).

Table 2: Schedule of Assessments

Study Visit Number **Study Visit Week**	**Visit 1** **Screening**[a]	**Visit 2** **Baseline**	**Visit 3** **Day 4**	**Visit 4** **Week 1**	**Visit 5** **Week 2**	**Visit 6** **Week 3**	**Visit 7** **Week 4** **or ET**[b]	**Visit 8** **Week 5**
Study Visit Day	**-14 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**7 ± 2days after Last Dose**
Study Visit Type	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient follow-up**[c]
Obtain informed consent	X							
Review inclusion/exclusion criteria	X	X						
Review randomization criteria		X						
Prior/concomitant medication review	X	X	X	X	X	X	X	X
Randomize (IXRS) to treatment		X						
Administration of study drug[d]		X	X	X	X	X		
Study drug accountability			X	X	X	X	X	
Clinical and Laboratory Evaluations								
Demography	X							
Medical history	X							
Psychiatric history/mental status	X							
SCID-CT[e]	X							
Physical and neurological examination	X						X	
Height	X							
Vital signs[f]	X	X	X	X	X	X	X	
Weight (including BMI)[g]	X	X			X		X	
Waist circumference		X					X	
Electrocardiogram (ECG)	X	X					X	
Hematology, chemistry, and urinalysis	X	X					X	
Serum prolactin	X	X					X	
Glycosylated hemoglobin (HbA_{1c})	X						X	

Table 2: Schedule of Assessments (Continued)

Study Visit Number **Study Visit Week**	**Visit 1** **Screening**[a]	**Visit 2** **Baseline**	**Visit 3** **Day 4**	**Visit 4** **Week 1**	**Visit 5** **Week 2**	**Visit 6** **Week 3**	**Visit 7** **Week 4** **or ET**[b]	**Visit 8** **Week 5**
Study Visit Day	**-14 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**7 ± 2days after Last Dose**
Study Visit Type	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient follow-up**[c]
Glucose and Lipid panel[h]	X	X					X	
Serum follicle stimulating hormone (FSH)[i]	X							
Serum human chorionic gonadotropin (β-hCG)	X							
Blood sample for pharmacogenomics (CYPP450 2D6)		X						
Blood sample for Population PK[j]		X					X	
Urine drug screen[k]	X	X					X	
Urine β-hCG[l]		X					X	
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	
Clinical Global Impression – Severity (CGI-S)	X	X	X	X	X	X	X	
Brief Negative Symptom Scale (BNSS)	X	X	X	X	X	X	X	
Montgomery-Asberg Depression Rating Scale (MADRS)		X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X
Barnes Akathisia Rating Scale (BARS)[m]	X	X	X	X	X	X	X	
Abnormal Involuntary Movement Scale (AIMS)[m]	X	X	X	X	X	X	X	
Simpson-Angus Scale (SAS)[m]	X	X	X	X	X	X	X	
Drug Effects Questionnaire (DEQ)		X					X	
Pittsburg Sleep Quality Index (PSQI)		X					X	
CogState Brief Battery (CBB)		X					X	

Table 2: Schedule of Assessments (Continued)

Study Visit Number Study Visit Week	Visit 1 Screening[a]	Visit 2 Baseline	Visit 3 Day 4	Visit 4 Week 1	Visit 5 Week 2	Visit 6 Week 3	Visit 7 Week 4 or ET[b]	Visit 8 Week 5
Study Visit Day	**-14 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**7 ± 2days after Last Dose**
Study Visit Type	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient follow-up[c]**
Pretreatment event monitoring	X							
Adverse events (AE) monitoring		X	X	X	X	X	X	X
Duplicate Subject Check[n]	X						X	X

Abbreviations: AE = adverse event; BARS = Barnes Akathisia Rating Scale; β-hCG = human chorionic gonadotropin; BMI = Body Mass Index; BNNS = Brief Negative Symptom Scale; C-SSRS = Columbia Suicide Severity Rating Scale; ET = early termination; FSH = Follicle stimulating hormone; IXRS = interactive response technology; MADRS = Montgomery-Asberg Depression Rating Scale; SAS = Simpson-Angus Scale; PANSS = Positive and Negative Syndrome Scale; PSQI = Pittsburg Sleep Quality Index; PK = pharmacokinetic; SCID-CT = Structured Clinical Interview for DSM-5, Clinical Trials Version.

[a] Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator.

[b] If a subject discontinues from the study, all Visit 7 procedures should be performed at the ET visit, within 48 hours of last study dose. All procedures and assessments scheduled for Visit 7 (Week 4) will be utilized as the Baseline procedures and assessments for the open-label extension study (SEP361-202).

[c] All subjects will have an inpatient/outpatient safety follow-up prior to discharge (7 [± 2]) days after their last dose of study drug.

[d] All study drug will be taken once daily in the evening by mouth.

[e] The SCID-CT will be used to support the DSM-5 diagnosis and must be administered by a qualified rater listed on Form 1572 with at least 2 years' experience with the population under study.

[f] Vital signs will include supine and standing measurements of blood pressure; and heart rate, respiratory rate, and oral body temperature.

[g] BMI will be calculated and recorded in the eCRF at the clinical site at Screening for other visits, BMI will be calculated during statistical analysis.

[h] Subjects must be fasted (no food or drink except water at least 8 hours prior to specified blood tests). Blood samples should be drawn in the morning followed by a snack or meal.

[i] Blood samples for follicle stimulating hormone (FSH) will be collected if menopause is suspected.

[j] Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected predose (prior to administration of the first dose) on Day 1; one postdose sample will be collected on Day 29. The time and date of the 3 previous doses of study drug, time, and date of sampling must be recorded. Time and date of food intake must be recorded on Day 29 when blood samples are collected for determination of SEP-363856 and SEP-363854 concentrations.

[k] If a subject is issued a day pass, an unscheduled urine drug screen will be performed upon returning to the site. Urine drug screen may be ordered at other visits as deemed clinically appropriate. These results should be discussed with the Medical Monitor.

[l] Any positive urine β-hCG test should be confirmed by a serum β-hCG test.

[m] Unscheduled BARS, AIMS, and SAS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment. See Section 10.3.

[n] Following the last contact with a subject, the duplicate enrollment system should be updated, as appropriate (US sites only).

Note: With the exception of SCID-CT and DEQ, all rating assessments will be performed by the rater using a tablet. In the event that a tablet is not available, the rating assessments will be performed by the rater using a paper version of the assessment.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BNSS	Brief Negative Symptom Scale
BOLD	Blood oxygen level dependent
BUN	Blood urea nitrogen
CDR	Clinical data repository
CFR	Code of Federal Regulations
CGI-I	Clinical global impression - improvement
CGI-S	Clinical global impression - severity
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia – Suicide Severity Rating Scale
CYP	cytochrome
DEQ	Drug Effects Questionnaire
ECG	Electrocardiogram
EDC	Electronic data capture
EEG	Electroencephalogram
ET	Early termination

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
FDA	U.S. Food and Drug Administration
fMRI	functional magnetic resonance imaging (fMRI)
GCP	Good Clinical Practice
5-HT	5-hydroxytryptamine (serotonin)
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPD	Important protocol deviation
IRB	Institutional Review Board
IXRS	Interactive voice/web response system
LOCF	Last Observation Carried Forward
LIMS	Laboratory information management system
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MID	Monetary incentive delay
mITT	Modified Intention-to-Treat
MMRM	Mixed-effects Models Repeated Measures
MoA	Mechanism of action
SAS	Simpson-Angus Scale
MTD	Maximum tolerated dose
N2	NREM sleep stage 2
N3	NREM sleep stage 3
NCS	Not clinically significant
NREM	Non-rapid eye movement sleep
PANSS	Positive and negative syndrome scale
PD	Pharmacodynamic(s)
PE	Physical examination
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
POPPK	Population pharmacokinetics

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
PR	Time between P wave and QRS in electrocardiography
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred term
QD	Once daily
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
REM	Rapid eye movement
RR	Respiration rate
SAD	single ascending dose
SAE	Serious adverse event
SCID-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SOC	System organ class
TAAR1	trace amine associated 1 receptors
US, USA	United States, United States of America
USP	United States Pharmacopeia
VAS	Visual analogue scale
WBC	White blood cells
WHO	World Health Organization

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled/randomized.
Study Drug (or Study medication) or Investigational Product	Term to cover investigational drug and placebo.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and was assigned a randomization number.
Enrolled Subject	Any subject who was successfully screened and enrolled into the pre-randomization period of the study.
Randomization Failures	Any subject who was enrolled but not randomized.
Completed Subject	Any subject who participated throughout the duration of the study, up to and including the last in-clinic visit.
Early Termination Subject	Any subject who was successfully screened and randomized into the treatment period of the study, but did not complete the study.
End of Treatment	The day that the subject receives protocol-defined last dose of the study drug. This may or may not include a taper period.
End of Study	The day that the subject completes the study per the study design.

4. INTRODUCTION

4.1. Background

Schizophrenia is a chronic and disabling neurodegenerative disorder characterized by a mixture of positive symptoms (eg, hallucinations, delusions, and thought and movement disorders), negative symptoms (eg, flat affect, anhedonia, alogia, and avolition), and cognitive deficits (eg, impaired memory, attention, and planning/organizing). Mood symptoms such as depression, anxiety, hostility, and excitement can also be present in patients with schizophrenia (Patel-2007; NIMH-2010). Despite scientific advances, schizophrenia remains one of the most challenging diseases to treat due to its variable nature, the heterogeneity of clinical response, the side effects of treatment, and its association with high morbidity and mortality (Lehman-2004; Tandon-2008; NIMH-2010).

Schizophrenia has an estimated population prevalence of approximately 1% (estimated 2.4 million adults), with a diagnosed prevalence of 0.51% in the United States (Narrow-2002; Wu-2006). It affects both genders equally (NIMH-2010) typically first manifesting in young adults, with the peak ages of onset in the early to mid 20s in men and late 20s in women (APA-2000). It is believed to be caused by a combination of genetic and environmental factors (Minzenberg-2008). Dopaminergic, serotonergic and glutamatergic systems are believed to play a role in schizophrenia (Kuroki-2008; Kim-2009).

The current standard of care for the treatment of schizophrenia is the use of second generation antipsychotics or "atypical antipsychotics" (Lehman-2004; Kreyenbuhl-2009; NIMH-2010; Meltzer-2011; Nakamura-2009). These "atypicals" are thought to have fewer extrapyramidal side effects compared to first generation antipsychotics or "typical antipsychotics" (eg, haloperidol) (Leucht-2009; Naber-2009). However some patients respond poorly to both atypical and typical antipsychotics and some continue to have symptoms and substantial functional/cognitive impairment (Keefe-2006; Webber-2008). Very few patients return to Baseline (pre-psychosis) function (Schultz-1999; Pearlson-2000; Kapur-2001). In addition, some atypical agents have a variety of other side effects, including weight gain, metabolic syndrome, sedation, QTc prolongation, extrapyramidal symptoms and tardive dyskinesia (Davis-2004; Lieberman-2005; Newcomer-2007; Leucht-2009), which may lead to significant medical problems as well as contribute to poor compliance and treatment discontinuation. The large scale NIMH-CATIE schizophrenia study found that 70% to 80% of outpatients discontinue medications because of lack of efficacy or occurrence of side effects (Lieberman-2005) often leading to relapse of symptoms and need for rehospitalization (Ascher-Svanum-2010; Munro-2011; Morken-2008). Clearly, an unmet need exists for new, effective, and well-tolerated treatments.

4.2. Study Conduct Rationale

SEP-363856 is a CNS-active compound, which shows broad efficacy in animal models of schizophrenia (positive and negative symptoms), cognition and depression. The molecular target responsible for the profile effects has not been completely elucidated, but may include actions at 5-HT1A and trace amine associated 1 (TAAR1) receptors. Rat electroencephalogram (EEG)

studies showed that SEP-363856 suppressed rapid eye movement (REM) sleep in a dose dependent manner. In nonhuman primate functional magnetic resonance imaging (fMRI) experiments, similar to risperidone, pretreatment with SEP-363856 also reduced the ketamine brain fMRI response in rhesus monkey supporting an antipsychotic-like profile. Taken together, these data demonstrate that SEP-363856 exhibits clear, functional CNS PD signals in rats and nonhuman primates.

To date, 210 subjects have received oral doses of SEP-363856 in six Phase 1 clinical studies. Five Phase 1 studies have been completed (SEP361-101, SEP361-103, SEP361-105, SEP361-106, and SEP361-108). One Phase 1 study has been clinically completed (SEP361-104). The first in human clinical study, a single ascending dose study (SAD; Study SEP361-101), was designed to determine the safety, tolerability, maximum tolerated dose (MTD), and PK of a single oral dose of SEP-363856 in normal, healthy, adult male subjects.

Study SEP361-103 was a randomized, double-blind, placebo-controlled, crossover polysomnography (PSG) study that investigated the effect of a single oral dose (50 mg and 10 mg) of SEP-363856 on REM sleep suppression and PK in healthy adult male subjects. A single 50 mg oral dose of SEP-363856 suppressed REM sleep in all subjects (increased latency to REM sleep and reduced time spent in REM sleep) and increased NREM sleep stage 2 (N2), and NREM sleep stage 3 (N3) (deep or slow wave sleep). A single oral 10 mg dose of SEP-363856 also increased latency to REM sleep to a lesser extent, but did not reduce time spent in REM sleep. Taken together, results from these 2 studies in healthy adult male subjects demonstrated acceptable safety profile as well as robust CNS effect.

Study SEP361-105 was a randomized, single-blind, placebo-controlled, SAD study assessing the safety, tolerability, and PK of SEP-363856 in male and female subjects with schizophrenia.

Study SEP361-106 was a 2-part, randomized, single-blind, placebo-controlled, multiple ascending oral dose (MAD) and open-label study in male and female schizophrenic patients assessing the safety, tolerability, and PK of SEP-363856 in the target patient population. Results from this study demonstrates an acceptable safety and tolerability profile of SEP-363856 up to 28 days in schizophrenia patients. Additionally, in Part 2, treatment with SEP-363856 at 75 mg/day for 28 days demonstrated improvement in efficacy measures (PANSS total score, CGI-S) compared with Baseline. Furthermore, ad hoc subgroup analyses showed a significantly greater decrease from Baseline in PANSS total scores at the end of the 28 day treatment period in subjects who had less frequent hospitalizations per year of illness compared with subjects who had more frequent hospitalizations per year of illness.

Study SEP361-104 was a randomized, double-blind, placebo-controlled, single dose study of the effects of SEP-363856 (50 mg) and amisulpride (400 mg) on BOLD-fMRI signal in healthy adult male and female subjects with high or low schizotype characteristics. Subjects with high schizotype characteristics and patients with schizophrenia share many similar features including positive, cognitive, negative and anhedonia symptoms, although in high schizotypes the features present in an attenuated form. In this study, fMRI was used in combination with a validated monetary incentive delay (MID) task to examine the single dose effects SEP-363856 on changes in reward processing. During the anticipation/motivational phase of the task, SEP-363856 modulated striatum, insula and orbitofrontal cortex brain activity, and fMRI effects of SEP-363856 were similar to those observed with the D2 antagonist amisulpride. During the outcome/hedonic phase of the task, SEP-363856 generally increased brain activity in core reward

areas (striatum, insula), whereas amisulpride decreased brain activity in these same regions. Taken together the overall pattern of activity during MID task performance support specific hypotheses for the potential of SEP-363856, a novel MoA molecule, to improve positive and negative symptoms of schizophrenia. Overall, the known molecular pharmacology profile, animal model evidence, and clinical experience in healthy adult male and female subjects, adult male and female subjects with high and low schizotype characteristics, and patients with schizophrenia provide further support to evaluate SEP-363856 as a potential treatment for schizophrenia.

The present study is designed to evaluate efficacy and safety of SEP-363856 50 and 75 mg/day for 4 weeks in adult male and female subjects with an acute exacerbation of schizophrenia.

4.3. Risk-Benefit Assessment

Overall, in previous clinical studies SEP-363856 was generally well-tolerated. The PK and safety profiles observed in adult subjects from completed Phase 1 clinical studies supports the evaluation of SEP-363856 50 to 75 mg/day in adults with schizophrenia.

Schizophrenia is a life-long disorder and despite advances in drug treatment many patients continue to experience symptoms with impaired quality of life. SEP-363856 has a different and novel mechanism of action not related to direct antagonism of the D2 receptor. If proven effective and safe, it may provide a s major advance in the treatment of patients with schizophrenia.

4.4. Hypothesis

4.4.1. Primary Hypothesis

Treatment with SEP-363856 in subjects with schizophrenia will result in a significant reduction in the PANSS total score at Week 4 when compared to placebo.

Let μ_{SEP} and μ_{PBO} represent the mean changes from Baseline at Week 4 in PANSS total score for the SEP-363856 and placebo arms, respectively. The following hypothesis will be tested to compare the mean change values between the SEP-363856 group and placebo group at Week 4:

H_0: $\mu_{SEP} = \mu_{PBO}$ versus H_1: $\mu_{SEP} \neq \mu_{PBO}$

5. STUDY OBJECTIVES

5.1. Primary Objective

To evaluate the efficacy of flexibly dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS).

5.2. Secondary Objectives

- To evaluate the efficacy of flexibly dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by:
  - Clinical Global Impression-Severity (CGI-S)
  - PANSS subscale scores (positive, negative, and general psychopathology)
  - Brief Negative Symptom Scale (BNSS)
  - Montgomery-Asberg Depression Rating Scale (MADRS)
- To evaluate the safety and tolerability of flexibly dosed SEP-363856 (50 or 75 mg/day) using:
  - physical examinations (PE)
  - 12-lead electrocardiograms (ECG)
  - vital signs
  - adverse event (AE) reports
  - clinical laboratory results
  - body weight and body mass index (BMI)
  - Columbia – Suicide Severity Rating Scale (C-SSRS)

5.3. Other Objectives

- To assess whether SEP-363856 is associated with extrapyramidal symptoms as measured by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS).
- To characterize the effects of SEP-363856 as measured by the Drug Effects Questionnaire (DEQ).
- To explore the subjective effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI).
- To assess the effects of SEP-363856 on cognition based on the CogState Brief Battery (CBB).

- To perform population pharmacokinetic (POPPK) analysis using plasma SEP-363856 concentrations.
- To characterize the relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods.
- To explore the impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on SEP-363856 plasma exposure.

6. STUDY ENDPOINTS

6.1. Primary Endpoint

Change from Baseline in PANSS total score at Week 4

6.2. Secondary Endpoints

- Change from Baseline in CGI-S score at Week 4.
- Change from Baseline in PANSS subscale scores at Week 4.
- Change from Baseline in BNSS total score at Week 4
- Change from Baseline in MADRS total score at Week 4.
- Proportion of subjects who achieve a response, defined as a 20% or greater improvement from Baseline in PANSS total score at Week 4.
- The incidence of overall AEs, serious AEs (SAEs) and AEs (or SAEs) leading to discontinuation.
- Absolute values and changes from Baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], 12-lead ECGs).
- Frequency of subjects with suicidal ideation or suicidal behavior using the C-SSRS.

6.3. Other Endpoints

- Change from Baseline in BARS, AIMS and SAS scores at Week 4.
- Absolute visual analogue scale (VAS) scores of the DEQ.
- Change from Baseline in PSQI score at Week 4.
- Change from Baseline in the CBB total score at Week 4.

7. INVESTIGATIONAL PLAN

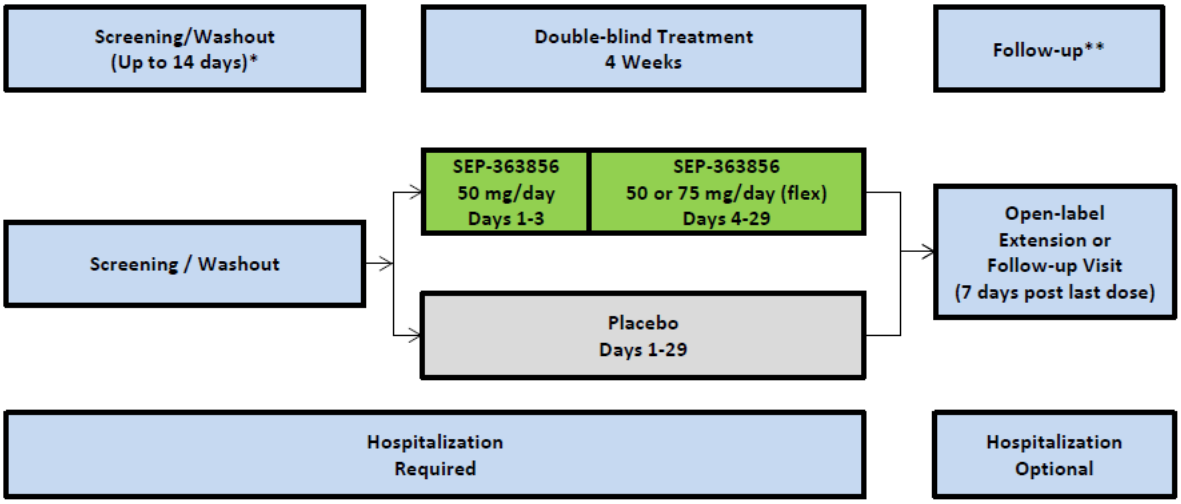
7.1. Overall Study Design

This is a multicenter, randomized, double-blind, parallel-group, flexibly-dosed, study evaluating the efficacy and safety of SEP-363856 in acutely psychotic adult subjects with schizophrenia using SEP-363856 (50 or 75 mg/day [ie, once daily]) versus placebo over a 4-week treatment period. This study is projected to randomize at least 240 subjects to 2 treatment groups (SEP-363856 or placebo) in a 1:1 ratio. Treatment assignment will be balanced within each clinical site. Subjects randomized to placebo will receive placebo treatment throughout the study. Study drug will be dosed at bed time with or without food.

The study will consist of 3 periods: Screening/Washout (up to 14 days), Treatment (4 weeks in-patient), and a Follow-up visit (7 days after last study drug dose for subjects who discontinue prior to Visit 7 or who complete the study but do not elect to enroll in the open-label extension study [SEP361-202]).

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2, Schedule of Assessments, and Section 11, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic



* Screening/washout period will be up to 14 days.

** Follow-up visit 7 ± 2 days after last dose only for subjects not continuing in to open-label extension study SEP361-202. Hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary

Screening/Washout Period (up to 14 days)

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days, during which they will be tapered off all psychotropic medications (except as noted in the protocol) in a manner that is consistent with labeling recommendations and conventional medical practices.

Subjects will remain hospitalized for the duration of the screening/washout period.

Double-Blind Treatment Period (4 weeks)

During the double-blind phase, subjects will be in-patient through Week 4. Subjects will be eligible for hospital discharge after the Week 4 visit (Day 29).

Randomization/Treatment: At double-blind Baseline (Day 1), subjects who have successfully completed the washout of prior medication (see Section 10.3.1) and have met the randomization criteria (see below) will be randomly assigned via interactive web/voice response system (in a 1:1 ratio) to one of two treatment arms: SEP-363856 or placebo. Study drug dosing will initiate the evening of the Baseline visit. Treatment will continue once-daily at night for the remainder of study during which procedures outlined in Table 2 will be conducted.

Subjects will receive SEP-363856 50 mg/day on Day 1 through 3. On Day 4, subjects are permitted (but not required) to titrate up to a dose of 75 mg/day. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits/weekly intervals starting from Visit 4 based on Investigator judgement. A dose reduction for tolerability purposes is permitted to occur more frequently than at weekly intervals. Subject can be flexibly dosed up until Visit 6, but no dose adjustments are allowed thereafter.

End of Double-Blind Period:

Subjects who complete the 4-week double-blind treatment phase will be eligible to participate in a separate open-label 26-week extension study (Study SEP361-202). Subjects who discontinue early from the study or complete the study and do not enter the 6-month extension study will be required to complete the follow-up visit 7 days (± 2 days) post last dose of study drug.

Upon completion or early discontinuation from the study, hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary. Prior authorization for the hospitalization must be approved by the Medical Monitor. After completion of the follow-up visit or upon study discontinuation, all subjects will be referred for appropriate continued treatment and follow-up care as determined by the Investigator.

Efficacy, Safety, and Pharmacokinetic Evaluations

Efficacy will be evaluated using the PANSS total and subscale scores, as well as CGI-S, BNSS, and MADRS scores. Effect of SEP-363856 on cognition will be assessed by the CBB.

Safety and tolerability will be monitored throughout the study by collection of PE results, ECGs, vital signs, AEs, clinical laboratory parameters, C-SSRS, body weight, and BMI. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation.

Subjects will provide information on subjective drug effects via administration of the DEQ. In addition, effects on movement disorders will be measured using the AIMS, BARS and SAS scales. Subjective effects on sleep will be measured by the PSQI scale.

Blood samples for plasma SEP-363856 and SEP-363854 concentrations will be collected on Day 1 (predose) and Day 29. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods exposure will be explored and reported separately. The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on plasma SEP-363856 exposure will be explored and reported separately.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

The randomization schedule will be generated by a non-study biostatistician. Once a subject is deemed eligible to be randomized at Day 1 (Visit 2), an IXRS will perform treatment assignment. Subjects will be randomized to one of the following treatment groups in a 1:1 ratio and balanced within each clinical site:

- SEP-363856 (50 or 75 mg/day flexible dosing for 4 weeks)
- Placebo (once daily for 4 weeks)

Once a randomization number has been assigned, it cannot be reused.

7.2.2. Blinding

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories (including imaging) will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods; (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of bioanalytical personnel involved in the analysis of PK samples; (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

Actual subject identity for plasma concentrations of SEP-363856 and SEP-363854 will not be disclosed before the database lock and the unblinding of the double-blind treatment phase.

7.2.3. Emergency Unblinding Procedures

In the case of a medical emergency, where knowledge of study drug by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IXRS. The date and reason for unblinding are to be documented in the source documents. Any subject for whom the treatment assignment was unblinded is to be discontinued from further study participation. The subject should return for a final study assessment as described in Section 11.8.6.

7.3. Rationale

7.3.1. Rationale for the Study Design

This is a multiregional, randomized, double-blind, parallel-group, flexibly-dosed study evaluating the efficacy and safety of SEP-363856 in acutely psychotic adult subjects with schizophrenia using SEP-363856 (50 or 75 mg/day) versus placebo over a 4-week treatment period. The 4-week study duration will provide an adequate timeframe within which to evaluate the effects of SEP-363856 compared to placebo in this subject population.

7.3.2. Rationale for the Dosages

Dosing of SEP-363856 50 or 75 mg mg/day for 28 days will be utilized in this study. Selection of these dose levels was guided by the maximum tolerated dose (MTD) determined for single doses of SEP-363856 administered to healthy adult male subjects in Study SEP361-101 (50 mg); the MTD determined for single doses administered to adult male and female subjects with schizophrenia in Study SEP361-105 (100 mg); by the single doses administered to healthy adult male subjects (Studies SEP361-103 and SEP361-104 [50 mg]) in which SEP-363856 was found to have robust CNS activity). In addition, dose selection is supported by acceptable safety and tolerability data from the 7-day (10 - 75 mg) and open label 28-day (75 mg) MAD study (Study SEP361-106, Parts 1 and 2) in adult male and female subjects with schizophrenia.

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study prior to study completion, the following study design and conduct elements are implemented:

- allowance of a dose reduction (from 75 to 50 mg/day) for drug tolerability purposes
- allowance of some concomitant psychotropic medications during study participation
- use of study centers with a good track record of enrolling and following eligible subjects
- train the study centers on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial
- monitor data collection at the site level for adherence during the study

Please see Section 15.3 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

To qualify for participation, subjects must meet all of the following inclusion criteria:

1. Subject must give written informed consent and privacy authorization prior to participation in the study. Separate consent will be obtained from a caregiver or legal guardian if required by local law.
2. Subject must be willing and able to comply with the study procedures and visit schedules, including required hospitalization for the washout period and the double-blind treatment period, and must be able to understand and follow verbal and written instructions.
3. Male or female subject between 18 to 40 years of age (inclusive) at the time of consent.
4. Subject meets DSM-5 criteria for schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the SCID-CT). The duration of the subject's illness whether treated or untreated must be ≥ 6 months.
5. Subject must have a CGI-S score ≥ 4 (moderate or greater) at screening and Baseline (Day 1).
6. Subject must have a PANSS total score ≥ 80 and a PANSS item score ≥ 4 (moderate) on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at screening and Baseline (Day 1).
7. Subject has an acute exacerbation of psychotic symptoms (no longer than 2 months).
   - Subject has marked deterioration of functioning in one or more areas, such as occupational, social, or personal care or hygiene.
   - Subject requires hospitalization for an acute psychotic exacerbation at the time of screening or has been hospitalized for the purpose of treating an acute psychotic exacerbation for no more than 2 consecutive weeks immediately before screening.

   Subjects who have been hospitalized for more than 2 weeks for reasons unrelated to an acute psychotic exacerbation may be included if such a hospitalization was for a condition other than an acute psychotic relapse. For example, subjects in a long-term hospital setting who have an acute exacerbation and are transferred to an acute unit are eligible for the study.
8. Subject has had no more than 2 prior hospitalizations for the treatment of an acute exacerbation of schizophrenia (not including the current hospitalization) This history must be confirmed based on report by a reliable informant (eg., caregiver or family member) or medical records available at the time of screening.
9. Subject's BMI must be at least 18 kg/m^2 but no more than 35 kg/m^2.
10. Female subject must have a negative serum pregnancy test at screening.
11. Female subject of reproductive potential agrees to remain abstinent or use highly effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken (See Section 21 Appendix II Highly Effective

Contraceptive procedures). In the Investigator's judgment, the subject will adhere to this requirement.

12. Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use highly effective methods of birth control (outlined in Section 21) from screening until at least 30 days after the last study drug administration.
13. Subject must be able and agree to remain off prior antipsychotic medication for the duration of the study.
14. Subject must have a total score < 5 on the SAS at Baseline (Day 1).
15. Subject is, in the opinion of the Investigator, generally healthy based on screening medical history, PE, neurological examination, vital signs, clinical laboratory values (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, and serum prolactin).
16. Subject has had a stable living arrangement at the time of screening and agrees to return to a similar living arrangement after discharge. This criterion is not meant to exclude subjects who have temporarily left a stable living arrangement (eg, due to psychosis). Such subjects remain eligible to participate in this protocol. Chronically homeless subjects should not be enrolled.
17. Subject must agree to comply with all restrictions for the required length of time (see Concomitant Medications and Restrictions in Section 10.3).

8.2. Subject Exclusion Criteria

To qualify for participation, subjects must not meet any of the following exclusion criteria:

1. Subject answers “yes” to “Suicidal Ideation” Item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at or during the Screening period (ie, in the past one month) and/or at Baseline (ie, since last visit).
2. Subject does not tolerate venipuncture or has poor venous access that would cause difficulty for collecting blood samples.
3. Subject is currently participating, or has participated in, a study with an investigational or marketed compound or device within 6 months prior to signing the informed consent, or has participated in 2 or more studies within 24 months prior to signing informed consent.
4. Subject has previously received SEP-363856.
5. Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that in the opinion of the Investigator, would limit the subject’s ability to complete and/or participate in the study:
    a. Hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular, hepatic, neurologic, or allergic disease that is clinically significant or unstable (except for untreated, asymptomatic, seasonal allergies at time of dosing).
    b. Subject has a history of neuroleptic malignant syndrome.

c. Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Pituitary tumors of any duration are excluded.
d. Disorder or history of a condition, or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, bowel resection, or any surgical procedure) that may interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH, or a clinically significant abnormality of the hepatic or renal system, or a history of malabsorption.
e. Subject has Alcohol or Substance Abuse Disorder (DSM-5 criteria). The only exceptions include caffeine or nicotine.
f. Subject has a clinically significant abnormal 12-lead ECG that may jeopardize the subject's ability to complete the study or a screening 12-lead ECG demonstrating any one of the following: heart rate > 100 beats per minute, QRS > 120 ms, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 ms (males), QTcF > 470 ms (females), or PR > 220 ms.
g. Subjects with known history of human immunodeficiency virus (HIV) seropositivity.

6. Female subject who is pregnant or lactating.
7. Subject who has a lifelong history or presence of symptoms consistent with a major psychiatric disorder other than schizophrenia as defined by DSM-5. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months), substance (other than nicotine or caffeine) use disorder within past 12 months, major depressive disorder, bipolar depression, mania, schizoaffective disorder, obsessive compulsive disorder, posttraumatic stress disorder. Previous or current symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms have not been a focus of primary treatment.
8. Subject tests positive for drugs of abuse at screening, however, a positive test for amphetamines, barbiturates, opiates, benzodiazepines may not result in exclusion of subjects if the investigator determines that the positive test is as a result of prescription medicine(s). In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the Investigator will evaluate the subject's ability to abstain from using this substance during the study. This information will be discussed with the Medical Monitor prior to study enrollment.
9. Subject is at significant risk of harming self, others or objects based on the Investigator's judgment.
10. Subject has attempted suicide within 3 months prior to screening.
11. Subject is involuntarily hospitalized.
12. Subject has received depot antipsychotics unless the last injection was at least one treatment cycle or at least 30 days (whichever is longer), prior to the screening phase.
13. Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents, given at adequate dose for at least 4 weeks within a 1 year period prior to Screening.

14. Subject has a history of treatment with clozapine for refractory psychosis and/or subject has been treated with clozapine (for any reason) within 4 months of Screening.
15. Subject is receiving a total dose of antipsychotic medication equivalent to ≥12.0 mg/day of haloperidol at Screening (see Section 22, Appendix III for table of haloperidol dose equivalents). Subject may be eligible if such treatment is less than 2 weeks in duration after consultation with the Medical Monitor.
16. Subject has received electroconvulsive therapy treatment within the 3 months prior to screening or is expected to require ECT during the study.
17. Subject takes or has taken other disallowed recent or concomitant medications (see Section 10.3). Subjects must taper off antipsychotic medications by Day -1.
18. Subject has a history of allergic reaction or suspected sensitivity to any substance that is contained in the formulation (gelatin).
19. Subject has any clinically significant abnormal laboratory values (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, and serum prolactin (Note: abnormal findings that may be clinically significant or of questionable significance will be discussed with the Medical Monitor prior to including subject).
20. Subject demonstrates evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation.

    Note: Subjects with serum alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 3 times the upper limit of the reference ranges provided by the central laboratory require retesting. If on retesting, the laboratory value remains ≥ 3 times the upper limit, the subject will be excluded.
21. Subject has a serum blood urea nitrogen (BUN) or serum creatinine (Cr) value ≥ 1.5 times the upper limit of normal for the reference range.
22. Subject has experienced significant blood loss (≥ 473 mL) or donated blood within 60 days prior to first dose of study drug; has donated plasma within 72 hours prior to the first dose of study drug or intends to donate plasma or blood or undergo elective surgery during study participation or within 60 days after the last study visit.
23. Subject has used disallowed prescription or disallowed nonprescription drugs, vitamins, or dietary or herbal supplements within 14 days prior to dosing or anticipates the need for any disallowed medication during their participation in this study [exception: female subjects who are taking oral, patch, or intrauterine device (IUD) hormonal contraceptives, or progestin implant or injection].
24. Subject is a staff member or the relative of a staff member.
25. Subjects with a fasting blood glucose at screening ≥ 126 mg/dL (7.0 mmol/L) or HbA_{1c} ≥ 6.5% will be excluded.
26. Subject has a prolactin concentration > 100 ng/mL at screening or has a history of pituitary adenoma. **NOTE:** Subjects with prolactin levels > 100 ng/mL and ≤ 200 ng/mL

at the Screening visit are permitted to enroll after discussion with the Medical Monitor to ensure exclusion of non-psychotropic drug-related causes of elevated prolactin levels.

27. .Subject is in the opinion of the Investigator, unsuitable in any other way to participate in this study.

8.3. Randomization Criteria

To qualify for randomization, subjects must meet all of the following randomization criteria:

1. Subject must have a PANSS total score ≥ 80 at Baseline (Day 1).
2. Subject must have a PANSS item score ≥ 4 on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at Baseline (Day 1).
3. Subject must not demonstrate a decrease (improvement) of ≥ 20% in the PANSS total score between Screening and Baseline visits (see Section 26 , Appendix VII for calculation of PANSS total score improvement), or the PANSS total score falls below 80 at Baseline (Day 1).
4. Subject must have a CGI-S score ≥ 4 at Baseline (Day 1).
5. Subject must have a total score < 5 on the SAS at Baseline (Day 1).
6. Subject must not answer “yes” to “Suicidal Ideation” Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Baseline (ie, since last visit).
7. Subject must meet all other inclusion and none of the exclusion criteria at Baseline (Day 1).

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

Table 5: Investigational Product

Attribute	Investigational Product		
Product name	SEP-363856	SEP-363856	Placebo
Dosage form	Capsule	Capsule	Capsule
Unit dose	50 mg	75 mg	NA
Route of administration	Oral	Oral	Oral
Physical description	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule
Excipients	None	None	Microcrystalline cellulose

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in one-week blister cards containing 9 capsules of SEP-363856 50 mg, 75 mg or Placebo capsules (7 days + 2 extra days).

9.2.2. Labeling Description

All packaging for the study drugs will be labeled with:

- Protocol number
- Sponsor's name and address
- Compound/Code or name of investigational drug and dosage form
- Contents (eg number of capsules)
- Investigational Drug/caution statement
- Instructions for use and storage
- Batch number
- Blank space to record visit number
- Blank space for subject identifiers
- Period of use (as required)
- Unique medication/kit ID number

- Investigator information (if needed)

9.3. Study Drug Storage

All study medication should be stored at United States Pharmacopeia (USP) controlled room temperature 20°C to 25°C (68°F and 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).

9.4. Dispensing of Study Drug

An Interactive Response System (IXRS) will be used to manage subject screening and randomization. The IXRS is an integrated web-based subject and drug management system.

Study drug blister cards will be assigned by the IXRS based on the treatment schedule and dose adjustment criteria. The IXRS will generate instructions for which study medication unit/number to assign to a subject.

Study drug will be administered to the subjects on an in-patient basis. Subjects will take one capsule of study drug per day at approximately the same time each evening at bed-time. Study drug may be taken without regard for food.

Study drug should be maintained under the strict control of qualified site staff at all times. Appropriate guidelines should be followed in proper dispensation to the study participant. Proper handling and storage should be followed. IXRS drug dispensing guidelines should be followed for dispensing study drug to the subject, in addition to all accountability records where required. Specific User Manuals will be supplied.

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the study drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/contract research organization (CRO).

Upon receipt of study drug, the Investigator or designee will inventory the supplies and verify receipt of supplies. The site will perform an acknowledgement of receipt via the IXRS, confirming the date of receipt, inventory and condition of study drug received.

The Clinical Inventory Management System (CIMS) will be used for the accountability of the study drug at the clinical site. The Investigator or designee will maintain the inventory for accountability within CIMS, including study drug dispensation, return and availability of study drug received. The Investigator or designee will collect and document all used and unused study drug from study subjects at appropriate study visits.

9.6. Study Drug Handling and Disposal

Study drug will not be dispensed to any person who is not a study subject under this protocol.

The Investigator or designee is required to return all unused the study drug to the Sponsor or designee as instructed The Investigator or designee is required to maintain copies of study drug shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

10. TREATMENT OF SUBJECTS

10.1. Study Drug

All study drug doses will consist of capsule(s) containing either SEP-363856 or placebo (in order to maintain blinding) administered orally once daily.

Subjects may take study drug without regard for food at approximately the same time each evening at bed-time.

The date and clock time of food intake must be recorded on Day 29 when blood samples are collected for determination of plasma SEP-363856 and SEP-363854 concentrations.

10.1.1. Dosage Adjustment Criteria

Subjects randomized to placebo will receive placebo treatment throughout the study.

Subjects will receive SEP-363856 50 mg/day on Day 1 through Day 3. On Day 4, subjects are permitted (but not required) to titrate up to a dose of 75 mg/day. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits/weekly intervals starting from Visit 4 based on Investigator judgement. A dose reduction for tolerability purposes is permitted to occur more frequently than at weekly intervals. Subject can be flexibly dosed up until Visit 6, but no dose adjustments are allowed thereafter.

10.2. Treatment Compliance

The Investigator will record the dose of the study drug and the dates of the initial and final administration for each dose.

Compliance must be monitored closely and determined at each visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment and for the successful outcome of the study. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant. Evidence of noncompliance must be immediately reported to the Clinical Research Associate (CRA) and/or Medical Monitor.

10.3. Concomitant Medications

The following information on all medication administered between Visit 1 (screening) and Visit 8 or at discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

Information on the format and version of coding dictionary is provided in the Data Management Plan (DMP). All medications will be coded using World Health Organization – Drug Dictionary (WHO-DD).

Table 6: Concomitant Medications/Therapies: Use During Study

Type of Drug	From Screening to Washout Phase	During Washout Phase	During Double-blind Treatment Phase
Antipsychotic drugs other than study drug	Taper	Not Permitted	Not Permitted
Mood stabilizers, antidepressants, or antiepileptic drugs	Taper	Not Permitted	Not Permitted
Fluoxetine or MAO inhibitors	Not Permitted	Not Permitted	Not Permitted
Clozapine	Not Permitted	Not Permitted	Not Permitted
Investigational products for other clinical or post-marketing studies	Not Permitted	Not Permitted	Not Permitted
Electroconvulsive therapy	Not Permitted	Not Permitted	Not Permitted
Antiparkinsonian drugs	Permitted[a]	Permitted[a]	Permitted[a]
Anti-anxiety and sedative hypnotic agents	Permitted[a]	Permitted[a]	Permitted[a]
Drugs for acute or mild, chronic medical conditions	Permitted[a]	Permitted[a]	Permitted[a]
Non-prescription pain medications	Permitted	Permitted	Permitted
Herbal supplements	Taper	Not Permitted	Not Permitted

Abbreviations: MAO = Monoamine oxidase.
[a] Permitted doses of these medications are specified in Section 10.3.2 and Section 10.3.3.

10.3.1. Prior Medications

Prior treatment with antipsychotic agents must be discontinued in a manner consistent with general medical practice during the screening period for at least 3 days. Depot neuroleptics must be discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to the screening visit.

Prior treatment with antidepressants must be discontinued as tolerated and clinically appropriate as follows:

- MAO inhibitors – at least 14 days prior to baseline (Day 1)
- Fluoxetine hydrochloride – at least 28 days prior to baseline (Day 1)
- Clozapine – at least 120 days prior to screening

Prior treatment with mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine, etc.) must be discontinued as tolerated and clinically appropriate at least 7 days prior to double-blind Baseline. All other psychotropic medication (except as described in this section), including antipsychotic medication, must be discontinued, as tolerated and clinically appropriate, prior to randomization in a manner that is consistent with labeling recommendations and conventional medical practice.

10.3.2. Concomitant Nonpsychotropic Medications

Medications for short-term treatment of an acute medical condition are allowed after consultation with the Medical Monitor. Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after randomization if the dose and regimen have been stable (± 25%) for at least 30 days prior to screening. The concomitant medication dose may change, as needed, after randomization (or be discontinued). β-adrenergic antagonists used to treat stable hypertension may be continued through the screening phase and post-randomization. In addition, use of non-prescription pain medications (eg, aspirin, acetaminophen) are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study drug. Female subjects may use oral, patch, or intrauterine device [IUD] hormonal contraceptives, or progestin implant or injection (detailed information on allowed contraceptives will be defined in Section 21).

10.3.3. Concomitant Psychotropic Medications

All antidepressants and mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine, etc.) are not allowed during the study.

Treatment with benztropine (benzotropine outside the US) up to 6 mg/day will be permitted, as needed, for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with propranolol (up to 120 mg/day) will be permitted as needed for akathisia.

Medications used to treat movement disorders should not be given prophylactically.

Concomitant use of lorazepam, temazepam, eszopiclone, zopiclone, zaleplon, zolpidem and zolpidem CR is permitted at the discretion of the Investigator with the following restrictions:

- lorazepam (or equivalent benzodiazepine) is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular lorazepam is permitted up to 4 mg/day for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per investigator judgment.
- temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day for males; ≤ 5 mg/day for females), and zolpidem CR (≤ 12.5 mg/day for males; ≤ 6.25 mg/day for females) may be administered at bedtime for insomnia, as needed.
- hypnotic agents should be administered no more than once nightly and should not be used in combination.

The date and clock time of the last dose of any concomitant psychotropic medication(s) taken prior to scheduled efficacy assessments must be recorded at each visit. Subjects should be encouraged to avoid taking these medications within 8 hours of scheduled assessments.

Opioids may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor.

Medications used for the treatment of anxiety/agitation and insomnia (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other). In regions that do not have the specified drugs available, similar drugs at equivalent dosages will be permitted as described in the Operations Manual or in consultation with the Medical Monitor.

Subjects who require treatment with one or more of the restricted concomitant medications (including other antipsychotics or anxiolytics [lorazepam or equivalent above protocol-specified limits]) will be discontinued (as appropriate) from the study.

10.3.4. Prohibited Medications

All antipsychotics (except for study drug treatment), antidepressants and mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine, lamotrigine, etc.) are not permitted during the study.

Subjects who require treatment with one or more of prohibited concomitant medications (including antipsychotics [other than study drug treatment] or anxiolytics [lorazepam or equivalent above protocol-specified limits]) will be discontinued (as appropriate) from the study. Limited use of these medications immediately prior to study discontinuation is permitted and will not constitute a protocol deviation.

10.3.5. Restricted Therapies

Subjects must not receive electroconvulsive therapy treatment within the 3 months prior to screening or is expected to require ECT during the study.

10.4. Other Restrictions

Subjects must abstain from alcohol from clinic admission through the end of the study.

10.5. Description of Study Periods, Hospital Discharge, and Day Passes

10.5.1. Description of Study Periods

The periods of the study, their duration, and subject status are provided below in Table 7.

Table 7: Description of Study Periods

Study Period	Visit Number	Study Day	Inpatient/Outpatient
Screening/Washout	Visit 1	-14 to -1	Inpatient
Double-blind Baseline	Visit 2	1	Inpatient
Double-blind	Visit 3	4	Inpatient
Double-blind	Visit 4	8	Inpatient
Double-blind	Visit 5	15	Inpatient
Double-blind	Visit 6	22	Inpatient
Double-blind	Visit 7	29	Inpatient (Subject may be discharged starting this visit)

Table 7: Description of Study Periods (Continued)

Study Period	Visit Number	Study Day	Inpatient/Outpatient
Follow-up	Visit 8	7 days after last dose (subjects who discontinue early or do not elect to enroll in Study SEP361-202)	Inpatient optional (Investigator discretion)

10.5.2. Hospital Discharge During the Study

To facilitate enrollment of acutely ill subjects and to optimize treatment compliance, hospitalization period is mandated during screening and the double-blind phases. Subjects are eligible for hospital discharge beginning on study Visit 7 (Day 29) or upon early termination if they meet all of the following criteria:

1. The subject is considered by the Investigator to be clinically stable and appropriate for discharge to an outpatient or community setting.
2. There is no evidence of imminent danger to self or others.
3. Subject answers "no" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) and Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS at time of evaluation.
4. An outpatient environment is available that ensures continued safety for the subject and continued contact with the treatment team for the remainder of the protocol.

Discharge under these conditions is permitted after completion of all assessments at Visit 7 (Day 29). Subjects may participate in day-hospital or outpatient programs after hospital discharge. If the subject does not meet the discharge criteria at Visit 7 or early termination; hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary. Prior authorization for the hospitalization must be approved by the Medical Monitor. After completion of the follow-up visit or upon study discontinuation, all subjects will be referred for appropriate continued treatment and follow-up care as determined by the Investigator.

10.5.3. Emergency Day Passes

Day pass may be granted during the study due to emergency unavoidable personal reasons with prior approval from the Medical Monitor. The pass must be of limited duration, and the subject must be accompanied by a staff member, family member, or caregiver. The subject must be considered by the Investigator to be clinically stable and Investigators should follow standard local facility or institutional procedures to ensure subject safety during the pass. The reason for and duration of the day pass as well as Medical Monitor approval must be documented. Subjects will receive an unscheduled urine drug screen upon return to site.

10.6. Guidance for Overdose

Potential overdose to SEP-363856 has not been evaluated. Appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the subject recovers. Consider the possibility of multiple-drug overdose.

10.7. Dietary Guidelines

While subjects are confined to the clinic, meals and snacks will be provided at the discretion of the clinical site. The date and clock time of food intake will be recorded.

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. A summary of assessments to be conducted at each visit is presented in Table 2.

11.1. Demographics and Baseline Characteristics

Demographics (date of birth, sex, ethnicity, race), prior and current medications, and medical and psychiatric history will be collected.

A medical history will be obtained by the Investigator or qualified designee as listed on the Form FDA 1572. If the subject's historical medical care was provided at another institution or location, documented efforts must be made to obtain these outside records to verify that the subject meets all inclusion and none of the exclusion criteria. This must be accomplished during the screening period. Alcohol and substance abuse history should also be obtained and documented in the subject's study chart. The Medical History will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For US sites only. At screening subjects will be checked for multiple study enrollment by clinical site staff using available registries of subjects participating in clinical trials. US sites will be provided training.

11.2. Prior and Concomitant Medication Review

See Section 10.3 for a complete description of medications permitted during the study. Site study staff will record all medications used to treat schizophrenia taken within 1 month prior to screening visit in the eCRF. Also, the following parameters will be recorded for all concomitant medications: drug name, route of administration, total daily dose, unit, frequency, start/stop dates, indication, and whether the medication was started after last dose of study medication. The prior and concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

11.3. Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version (SCID-CT)

The SCID-5-CT is a modified version of the SCID developed for use in clinical trials. It is a semi-structured interview for the purpose of making a DSM-5 diagnosis (First-2015). Clinicians administering the SCID should be familiar with the DSM-5 classification and diagnostic criteria. The SCID-5-CT will be administered by a qualified rater at the research site listed on Form FDA 1572 with at least 2 years of experience with the population under study. The administration time is approximately 30 - 40 minutes.

11.4. Efficacy Assessments

11.4.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 scales: the Positive scale assesses hallucinations, delusions, and related symptoms; the Negative scale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology scale addresses other symptoms such as anxiety, somatic concern, and disorientation. An anchored Likert scale from 1 - 7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item. Individual items are then summed to determine scores for the 3 scales, as well as a total score. A Composite scale score (Positive scale score minus Negative scale score) can also be calculated to show the relative valence of positive and negative symptoms. Total time required for the PANSS interview and scoring is approximately 30 - 40 minutes (Kay-1994, Opler-1992; Perkins-2000). PANSS raters will be required to meet specific training and education criteria before they are certified to rate for this study. In addition, raters will receive specific training and education regarding all of the assessments prior to study initiation.

11.4.2. Brief Negative Symptom Scale (BNSS)

The BNSS is a rating scale to measure the current level of severity of negative symptoms in schizophrenia and schizoaffective disorder. The measure is comprised of 13 individual items and 5 domain scores (blunted affect, alogia, avolition, anhedonia, and asociality). The 5 domain scores provide a summary score and the 13 individual items provide a composite total score (ranging from 0 to 78). Each of the items are scored on a Likert-type 7-point scale from 0 - 6, where values of 0 indicates symptom is absent and a value of 6 means the symptom is a severe form. The number of items varies per domain. BNSS raters will be required to meet specific training and education criteria before they are certified to rate for this study. In addition, raters will receive specific training and education regarding all of the assessments prior to study initiation.

11.4.3. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. The Structured Interview Guide for the MADRS (SIGMA) (Williams-2008) will be used for the administration of the MADRS assessment. The MADRS will be administered by a qualified rater at the site.

11.4.4. Clinical Global Impressions – Severity Scale (CGI-S)

The CGI-S is a clinician-rated assessment of the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity. Following a clinical interview, the CGI-S can be completed in 1 to 2 minutes. The CGI-S will be administered by a qualified rater at the site.

11.4.5. CogState Brief Battery (CBB)

The CBB scale assesses four domains. The Detection test (Attention Domain) measures speed of performance. The mean of the log10 transformed reaction times for correct responses are utilized to determine the score. Lower scores correspond to better performance. The Identification test (Information Processing Domain) also measures speed of performance. The mean of the log10 transformed reaction times for correct responses are utilized to determine the score. Lower scores correspond to better performance. The One Card Learning test (Visual Learning Domain) measures accuracy of performance. Arcsine transformation of the proportion of correct responses are utilized to determine the domain score. Higher scores correspond to better performance. The One-back Memory test (Working Memory Domain) measures Arcsine transformation of the proportion of correct responses are utilized to determine the domain score. Higher scores correspond to better performance.

11.5. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct.

11.5.1. Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, “Has there been any change in your health status since your last visit?”). See Section 12, Safety Reporting.

Pretreatment events will be monitored at Visit 1.

AEs and SAEs will be monitored from Visit 2 onward.

11.5.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 23, Appendix VI.

Blood and urine samples will be collected for clinical laboratory tests. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA) and/or other laboratory certifications or equivalent accreditation documents.Any POC (point of care) kits that are performed on site by study personnel rather than in a lab- must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.5.3. Vital Signs

Supine systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature will be measured following 5 minutes of seated rest.

Blood pressure and pulse rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and pulse rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate

throughout the study. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

11.5.4. Electrocardiograms (ECGs)

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. Refer to Section 20 Appendix I for additional information. ECG parameters to be collected include ventricular heart rate (beats/min), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec), and overall ECG interpretation (Normal, Abnormal NCS, Abnormal CS).

It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility for or continuance in the study. Abnormalities require comment as NCS or CS. Typically, CS designated events will be reported as adverse events.

ECGs will be reviewed, signed and dated by the Investigator after each ECG collection. The same physician should review all ECG reports for a given subject whenever possible.

The original ECG tracing will be kept with subject's source documentation. A copy may be collected by the Sponsor.

11.5.5. Physical and Neurological Examination

A full PE as well as a neurological will be performed. The PE includes 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).

All PE and neurological exam findings at screening will be captured in the medical history in the CRF. Any clinically significant changes from screening, as determined by the Investigator, will be noted as AEs in the CRF.

11.5.6. Height, Weight, and BMI

Weight will be measured in kilograms at Visit 1 (Screening), Visit 2 (Baseline), Visit 5 (Day 15), and Visit 7 (Day 29). Height in meters will be recorded only at Visit 1 (Screening).

Height will be measured without shoes.

Weight will be measured in street clothes, without shoes and coat/jacket.

BMI will be calculated by site staff using the equation BMI = weight [kg]/height [m]^2 at Screening (Visit 1) only. BMI for all other visits will be derived within the Electronic Data Capture (EDC) system.

Waist circumference will be measured in inches or centimeters and recorded in the eCRF.

11.5.7. Safety Scales

11.5.7.1. Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk. There are two items related to dental status, as well as three global impression items assessing overall severity, incapacitation, and the subject's awareness of abnormal movements (Guy-1976; Munetz-1988). The AIMS raters will be required to meet specific credential and educational criteria before they are certified to rate for this study. The AIMS will be administered by a qualified rater at the site.

11.5.7.2. Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale geared toward assessment of neuroleptic-induced akathisia, though it can be used to measure akathisia associated with other drugs as well. The BARS consists of four items, including one item assessing objective restlessness, two items targeting subjective restlessness (awareness and related distress), and one global clinical assessment item. All items are anchored and utilize a 4-point scale, except for the global rating which has a 6-point scale (from absence of akathisia through severe akathisia). The subjective and objective items are summed to yield a total score. The BARS can be administered in about 10 minutes (Barnes-1989; Barnes-2003). The BARS will be administered by a qualified rater at the site.

11.5.7.3. Simpson-Angus Scale (SAS)

The SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale of severity, and address rigidity, gait (bradykinesia), tremor, akathisia, shoulder shaking, glabellar tap, and salivation (Siddiqui-2009; Simpson-1970). The SAS will be administered by a qualified rater at the site.

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

The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the trial. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site. Subjects with Type 4 or Type 5 suicidal ideation during the study will be discontinued from the study and referred to a mental health professional (Posner-2007). At screening visit, "Baseline/Screening" version of C-SSRS will be used. For all visits from Visit 2 onward, the "Since Last Visit" version of the C-SSRS will be used.

11.5.7.5. Drug Effects Questionnaire (DEQ)

A Drug Effects Questionnaire designed to assess subjective effects will be completed by the subject. The DEQ consist of 3 questions scored on a visual analog scale (VAS).

11.5.7.6. Pittsburg Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) consists of 19 self-rated questions used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month (Buysse-1989).

11.6. Population Pharmacokinetic Assessments

All blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be obtained at the same time that other blood samples are taken whenever possible. Placebo samples will not be analyzed. The time and date of the 3 previous doses of study drug, date, and clock time of sampling must be recorded. Date and clock time of food intake must be recorded on Day 29 when blood samples are collected for determination of plasma SEP-363856 and SEP-363854 concentrations. Plasma SEP-363856 and SEP-363854 concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SEP-363856 exposure will be explored using population PK/pharmacodynamics (PD) methods, and reported separately. The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on SEP-363856 plasma exposure will be explored and reported separately. See Section 24, Appendix V for details including instructions of processing blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations.

11.7. Pharmacogenomic Assessments

If a subject has consented to have a deoxyribo nucleic acid (DNA) sample taken for genetic analysis (and is eligible for randomization), a blood sample (approximately 4 mL) for pharmacogenetic (PGx) analysis will be taken at Visit 2 (Baseline). Samples should not be collected if the subject has not consented to PGx sampling. If samples are collected for analysis, this analysis must be performed. The timing of the analysis may be following completion of this study and as such can be reported separately. Blood samples will be shipped to the central laboratory where they will be stored frozen until shipment to the PGx laboratory (contact details provided in the general study information section of the protocol). Following shipment, DNA will be extracted and the PGx laboratory will remain blinded to the identity of the subject, but will have access to information relating to demographics of the subject (ethnic origin and gender). See Section 25 Appendix VI for details including instructions of PGx sample handling.

11.8. Study Visits and Assessments

See Table 2 Schedule of Assessments, for a summary of procedures at each study visit. See Section 11.1 to Section 11.5 for detailed information on conducting assessments.

11.8.1. Screening: Visit 1 (Day -14 to -1);Inpatient

A unique screening number will be assigned to each subject.

The subject's eligibility assessment will be reviewed by the contract research organization's (CRO) oversight quality team along with the sponsor based on protocol specified inclusion and exclusion criteria. The sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility and will be copied on all communications between the CRO and the site. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled.

Subjects will be evaluated at the screening visit (1 to 14 days before the first dose of study drug) to determine their eligibility for the study. The following procedures will be conducted during this visit:

- Obtain signed informed consent and privacy authorization from the subject before conducting any other visit procedures.
- Inclusion and exclusion criteria
- Obtain demographic information
- Prior/concomitant medications
- Pretreatment events
- Medical history
- Psychiatric history/mental status
- SCID-CT
- Physical and neurological examination including height and weight; clinical site staff to calculate and record BMI
- Vital sign measurements (prior to ECG)
- Perform ECG
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel, and lipid panel).
- Blood samples for serum pregnancy test (serum human chorionic gonadotropin [β-hcG]) for female subjects and serum follicle stimulating hormone (FSH) for female subjects if menopause is suspected.
- Urine sample for urinalysis and urine drug screen (UDS)
- Duplicate subject check
- PANSS
- BNSS
- C-SSRS
- CGI-S
- AIMS

- BARS
- SAS

Procedures should be completed in the following sequence.

Screening Visit	**Visits 2 through Visit 8**
1. SCID-CT (study center rater)	1. PANSS (study center rater)
2. PANSS (study center rater)	2. BNSS (study center rater)
3. BNSS (study center rater)	3. MADRS (study center rater)
4. C-SSRS (study center rater)	4. C-SSRS (study center rater)
5. CGI-S (study center rater)	5. CGI-S
	6. AIMS/BARS/SAS
	7. PSQI
	8. DEQ
	9. CBB

Note: With the exception of SCID-CT and DEQ, all rating assessments will be performed by the rater using a tablet. In the event that a tablet is not available, the rating assessments will be performed by the rater using a paper version of the assessment.

Subjects found to be ineligible during Visit 1 will not be required to complete all the Visit 1 assessments and will not be followed up on leaving the study.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator.

Re-screened subjects will be re-consented and all Visit 1 procedures will be repeated.

11.8.2. Baseline: Visit 2 (Day 1); Inpatient

The following procedures will be conducted during this visit:

- Review inclusion and exclusion criteria and randomization criteria.
- Prior/concomitant medications.
- Randomize to treatment
- Blood sample for determination of plasma SEP-363856 and SEP-363854 (pre-dose)
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG.
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glucose panel and lipid panel).

- If subject signed separate genetic informed consent, collect blood samples for pharmacogenomics (CYPP450 2D6)
- Urine sample for urinalysis, UDS, and β-hcG (for female subjects).
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI
- DEQ
- CBB
- Administer study drug
- Adverse events

11.8.3. Visit 3 (Day 4); Inpatient

The following procedures will be conducted during this visit:

- Concomitant medications.
- Perform study drug accountability
- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- Administer study drug
- Adverse events

11.8.4. Visit 4 (Week 1; Day 8), Visit 5 (Week 2; Day 15), and Visit 6 (Week 3; Day 22); Inpatient

The following procedures will be conducted during each visit (unless otherwise specified):

- Concomitant medications.
- Perform study drug accountability
- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- Administer study drug
- Adverse events

11.8.5. Visit 7 (Week 4; Day 29/Early Termination); Inpatient

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability
- Physical and neurological examination including
- Weight and waist circumference
- Vital sign measurements (prior to ECG).
- Perform standard 12-lead ECG.
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel, and lipid panel).
- Blood sample for determination of plasma SEP-363856 and SEP-363854 concentration (post dose)
- Urine sample for urinalysis, UDS, and β-hcG (for female subjects).
- PANSS
- BNSS

- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI
- DEQ
- CBB
- Adverse events
- Duplicate subject check

At this visit, subjects who have completed treatment will have the option to enroll and continue treatment for an additional 26 weeks in an open-label extension study (Study SEP361-202). For subjects entering the extension study, Week 4 in this study will be Baseline for the extension study and subjects will not need to return for further visits in this study.

Subjects who do not enter the extension study will complete the inpatient follow-up period.

11.8.6. Visit 8 (+ 7 days); Inpatient Follow-up

All subjects who discontinue early or do not elect to enroll in the open-label extension study (Study SEP361-202) will have an inpatient/outpatient safety follow-up prior to discharge (7 ± 2 days) after their last dose of study drug. The following procedures will be conducted during this visit:

- Concomitant medications
- C-SSRS
- Adverse events
- Duplicate subject check

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the ICF and first drug administration are pre-treatment events. Those that occur after first administration of study drug are considered AEs.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from after first administration of study drug to the last study visit.The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a 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 at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the

result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. Laboratory reports will be initialed and dated on all pages by the Investigator.

Clinical Laboratory Tests Outside the Normal Range: Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during Screening is indicated as clinically significant and is not covered by the inclusion criteria in Section 8.1, the subject will **not** be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the Follow-Up Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalised or stabilised.

All on-site ECG tracings and ECG over-read reports will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

12.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All pre-treatment events and AEs/all AEs must be recorded on the CRF.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

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

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.
- **Dose Reduced.**
- **Dose Increased.**
- **Dose Not Changed**
- **Not Applicable.**
- **Unknown**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**

- **Not related -** Improbable temporal relationship and is plausibly related to other drugs or underlying disease.

- **Related**
  - **Possible** - occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after first administration of study drug through 30 days following the last dose of the study drug, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs “spontaneously” to PPD-PVG if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG within 24 hours of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. PPD-PVG provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board

(IRB) or Independent Ethics Committee (IEC) by the Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

For the UK, the appropriate Pharmacovigilance (PVG) group must be contacted immediately upon first knowledge of the incident. The immediate report should be made by the Investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event or pregnancy.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 90 days following the last dose of the study drug will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to commence discontinuation of the study drug. Further, the subject (or female partner of male subject) will be instructed to return promptly/within 48 hours of the first notification of pregnancy to the study center and undergo a serum/urine pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study drug. All pregnancies, whether or not the subject received any additional study drug, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG within 24 hours of the Investigator or study center staff becoming aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

If the subject received blinded study drug, unblinding of the study drug will be offered to the subject when knowledge of such treatment may have an impact on further treatment decisions. Otherwise, information regarding to what treatment the subject was assigned may be provided when the study has ended.

Pregnancy itself 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 or other AEs were detected.

13. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

13.1. Criteria for Study Drug Discontinuation

Subjects may be discontinued from the study drug at any time for any of the following reasons:

- Adverse event (specify)
- Lack of efficacy (specify)
- Withdrawal by subject (specify)
- Non-compliance with study drug (specify)
- Protocol deviation (specify)
- Death
- Progressive disease
- Pregnancy
- Other (specify)

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study drug.

The reason and information on the epoch for study drug discontinuation will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

13.2. Clinical Assessments After Study Drug Discontinuation

Subjects who have not received study drug will not be followed up on leaving the study.

For subjects who have received study drug and who prematurely discontinue from the study treatment (ie, do not complete through Visit 7), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.8.5.

Subjects who complete the study but do not elect to enroll in the open-label extension study (Study SEP361-202) and those subjects who discontinue the study early will complete a follow up visit 7 (±2) days after the last visit to assess any post study discontinuation adverse effects as described in Section 11.8.6.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center or at multiple centers for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study drugs pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects will undergo final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.8.5 and safety follow-up visit as described in Section 11.8.6.

15. STATISTICS

15.1. Sample Size

A sample size of 100 subjects per treatment group (SEP-363856 and placebo) will provide 80% power to detect a treatment effect size of 0.4 in change from Baseline in PANSS total score at Week 4 for SEP-363856 versus placebo, using a two independent sample t-test method with 2-sided significant level of 0.05. A clinically meaningful effect size of 0.4 was estimated based on review of published studies of other antipsychotics for the short-term treatment of schizophrenia. It is anticipated that 17% of all randomized subjects will discontinue early from the study. An upward adjustment of the sample size is thus used to compensate for missing data from subjects who are randomized and discontinue from the study. The total sample size will be 240 randomized subjects (or 120 subjects per treatment group).

15.2. Analysis Populations

15.2.1. Modified Intention-to-Treat Population

The modified intention-to-treat (mITT) population will consist of all subjects who are randomized, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline efficacy measurement in PANSS or CGI-S. Subjects will be included in the mITT population regardless of any protocol deviation. The mITT population will be the primary population for the efficacy analyses. Subjects will be analysed according to randomised treatment group.

15.2.2. Per Protocol Population

The per protocol (PP) population will consist of all mITT population subjects who satisfy the following conditions:

- Received assigned study medication as randomized
- Have 14 days or more continuous exposure
- Have 75%-125% compliance, both limit values inclusive
- Have no major protocol violations, determined by a blinded data review prior to database lock

Selected efficacy endpoints will be analyzed using the PP population.

15.2.3. Safety Population

The safety population will consist of all subjects who are randomized and have received at least one dose of study drug. Safety population will be the primary population for the safety analyses. Subjects will be analysed according to the actual treatment received (ie, placebo vs SEP-363856).

15.3. Data Analysis

15.3.1. Subject Disposition

Subject disposition will be summarized by the randomized treatment group (if applicable) and overall for all subjects. The number and percentage of subjects who are screened, screen-failed, randomized, and completed or discontinued the study (including reasons for discontinuation) will be presented. In addition, the number and percentage of subjects who will rollover to the open-label extension study (SEP361-202) in each treatment group and overall will be presented.

15.3.2. Drug Exposure and Compliance

Drug exposure and compliance will be summarized by treatment for the safety population. Drug exposure (in days) will be calculated as: last dose date - first dose date + 1. Exposure will be summarized both as a continuous variable for the double-blind period (i.e. mean days), and categorically:

- Number and percentage of subjects with drug exposure ≥ 4, ≥ 7, ≥ 14, ≥ 21, and ≥ 28 days;
- Number and percentage of subjects with drug exposure for 1 - 3, 4 - 6, 7 - 13, 14 - 20, 21 - 27, and ≥ 28 days

Percent compliance will be calculated by visit and overall for the double-blind period as: (number of capsules taken / number of capsules should have been taken) × 100%. Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the double-blind period. Subjects with missing compliance will not be classified as non-compliant. Compliance will be summarized both as a continuous variable (i.e. mean percentage) and categorically (i.e. number and percentage of subjects who are compliant vs. non-compliant, or with compliance < 75%, 75% - 125%, > 125%, and missing).

15.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potentially IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria.
- Received any disallowed concomitant medication.
- Have overall double-blind compliance rate < 75% or > 125%.

Individual IPDs will be presented for all randomized subjects in a data listing. The number and percentage of subjects in the mITT population with IPDs will be summarized by the type of deviation and the randomized treatment group.

15.3.4. Demographic and Baseline Characteristics

Basic demographics (e.g. age, gender, race, ethnicity, etc.) will be summarized for all screened subjects by randomization status (i.e. randomized vs. not randomized). Demographic and Baseline characteristics will be summarized for the mITT population and safety population.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher, and will be summarized by treatment for the safety population by presenting the number and percentage of subjects with at least one condition in each system organ class (SOC) and preferred term (PT).

15.3.5. Efficacy Analyses

15.3.5.1. Primary Efficacy Endpoint Analysis

This section describes the primary analysis for the primary efficacy endpoint. Sensitivity analysis of this endpoint is described in Section 15.3.12.

The primary efficacy variable is the change from Baseline in PANSS total score at Week 4, for testing superiority of the SEP-363856 treatment group over the placebo group. This variable will be analyzed using a Mixed Model for Repeated Measures (MMRM), with change from Baseline in PANSS total score at each visit as the response variable. The MMRM model will include factors for treatment, visit (Day 4, Weeks 1, 2, 3, and 4; as a categorical variable), pooled center, and treatment-by-visit interaction, and include Baseline PANSS total score as a covariate. An unstructured covariance matrix will be used for the within-subject correlation. Kenward-Rogers approximation will be used to calculate the denominator degrees of freedom. Pooled centers will be generated by country.

In case the model above fails to converge, a spatial exponential covariance structure and a spatial power covariance structure will be assumed sequentially. The first covariance structure to yield convergence will be used in the analysis.

The primary analysis for the primary efficacy endpoint will be based on the observed data only. Missing observations will not be imputed.

15.3.5.2. Secondary Efficacy Endpoint Analysis

CGI-S score

The primary analysis for this endpoint is described here. Sensitivity analysis of this endpoint is described in Section 15.3.12.

Change from Baseline in CGI-S score at Week 4 will be analyzed using an MMRM model similar to that of the primary efficacy variable, with change from Baseline in CGI-S score at each visit as the response variable and Baseline CGI-S score as a covariate.

The primary analysis for this endpoint is based on the observed data only. Missing observations will not be imputed.

PANSS subscale scores

Change from Baseline in each PANSS subscale (positive, negative, and general psychopathology) score at Week 4 will be analyzed using an MMRM model similar to that of the primary efficacy variable, with the respective PANSS subscale score at Baseline as the covariate. In addition, as a supportive analysis, missing PANSS subscale data at Week 4 will be imputed using the last observation carried forward (LOCF) method, and the resulting efficacy variables will be change from Baseline in PANSS subscale scores at the Week 4 LOCF endpoint. These

variables will be analyzed using the analysis of covariance (ANCOVA) model which includes treatment and pooled center as fixed factors and the respective Baseline value as a covariate.

BNSS total score

Change from Baseline in BNSS total score at Week 4 will be analyzed using an MMRM model similar to that of the primary efficacy variable, with Baseline BNSS total score as the covariate. As an additional, supportive analysis, missing BNSS data at Week 4 will be imputed using the LOCF method and the resulting efficacy variable will be the change from Baseline in BNSS total score at the Week 4 LOCF endpoint. This variable will be analyzed using an ANCOVA model similar to the one above, including Baseline BNSS total score as a covariate.

MADRS total score

Change from Baseline in MADRS total score at Week 4 will be analyzed using an MMRM model similar to that of the primary efficacy variable, with Baseline MADRS total score as the covariate. As an additional, supportive analysis, missing MADRS data at Week 4 will be imputed using the LOCF method and the resulting efficacy variable is change from Baseline in MADRS total score at the Week 4 LOCF endpoint. This variable will be analyzed using an ANCOVA model similar to the one above, including Baseline MADRS total score as a covariate.

PANSS responders

Subjects who achieve a response are defined as those having a 20% or greater improvement in PANSS total score from Baseline at the Week 4 LOCF endpoint (i.e. missing PANSS data at Week 4 being imputed by the LOCF method). The percent improvement in PANSS total score from Baseline will be calculated by:

$$\frac{\text{PANSS total score at Week 4 LOCF endpoint - PANSS total score at Baseline}}{\text{PANSS total score at Baseline - 30}} \times 100\%$$

For each subject, the responder indicator will be set to 1 if the percent change is negative and the magnitude is equal to or greater than 20%. The indicator will be set to 0 if the percentage is negative but the magnitude is less than 20% or if the percentage is non-negative. The indicator will be set to missing if the percentage is missing.

PANSS responders will be analyzed using a logistic regression model with responder indicator as the dependent variable, and include treatment and geographic region as fixed factors and Baseline PANSS total score as a covariate.

15.3.5.3. Other Efficacy Endpoint Analysis

Change from Baseline in the CBB composite score at Week 4 will be analyzed using an ANCOVA model with treatment and pooled center as fixed factors and Baseline CBB composite score as a covariate. In addition, the LOCF ANCOVA analysis as described in Section 15.3.5.2 will be performed as a supportive analysis.

15.3.5.4. Adjustment for Multiplicity

No multiplicity adjustment will be performed in the testing of the efficacy endpoints.

15.3.5.5. Subgroup Analysis

Exploratory analyses will be performed on certain subgroups of interest for the primary efficacy endpoint of change from Baseline in PANSS score at Week 4 and the secondary endpoint of change from Baseline in CGI-S score at Week 4. The subgroup factors of interest will include: categorized age, gender, race, number of prior hospitalizations for treatment of schizophrenia, geographic region or country. Details of the subgroup analyses will be described in the SAP.

Summary statistics and MMRM analysis results will be provided by treatment for each subgroup. In addition, inferential analysis of treatment-by-subgroup interaction will be performed for each subgroup factor using the MMRM method on the two efficacy variables described above. The model will include treatment, visit (as a categorical variable), subgroup, pooled center, Baseline value, and treatment-by-visit, treatment-by-subgroup, subgroup-by-visit, and treatment-by-subgroup-by-visit interactions. Details of the subgroup analysis of efficacy data will be provided in SAP.

15.3.6. Safety Analyses

15.3.6.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher. AEs are untoward medical occurrences:

- that occurred on or after the first dose of study drug,
- with a missing start date and a stop date on or after the first dose of study drug, or
- with both a missing start and stop date.

AEs will be summarized by treatment and by MedDRA system organ class (SOC) and Preferred Term (PT).

The following AEs will be summarized and presented by treatment and by MedDRA SOC and PT for the Safety population:

- All AEs (including number of events and subject incidence).
- AEs by severity (mild, moderate, severe).
- AEs by relationship to the study treatment (related, or not related).

The following conventions will be followed in summarizing AEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- If a subject reports more than one AE within a preferred term and/or a body system, the AE with the highest known severity within each body system and within each preferred term will be included in the summaries by severity.
- For summaries by relationship to the study drug, AEs will be grouped as “related” or “not related.” AEs assessed as “possible,” “probable,” or “definite,” will be grouped as “related.” If a subject reports more than one AE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related.

Summaries of SAEs and AEs leading to discontinuation will also be provided. A listing of AEs, as well as a listing of deaths, SAEs, or AEs leading to discontinuation, will be presented.

15.3.6.2. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables, and by presenting summary statistics for the absolute values as well as the change from Baseline values by treatment. For laboratory parameters with categorical outcomes, the number and percentage of subjects with each outcome will be presented. The data listings will flag values outside the reference range.

The change from Baseline values will be analyzed by nonparametric rank ANCOVA to compare between the SEP-363856 and placebo treatments for: serum lipid (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), glucose, HbA_{1c} and prolactin levels. Details of the rank ANCOVA analysis will be provided in the SAP.

15.3.6.3. ECGs/Centrally-read ECG/Holter Monitor

Absolute values and changes from Baseline in ECG parameters will be summarized by treatment. In addition, the number and percentage of subjects with elevated QTc intervals (> 450 msec, > 480 msec, and > 500 msec) and changes in QTc intervals ≥ 30 msec and ≥ 60 msec will be summarized by treatment. Fridericia's correction (QTcF) and Bazett's correction (QTcB) will be used for QT interval correction.

15.3.6.4. Vital Signs

Vital sign parameters, as well as weight and BMI, will be summarized by presenting summary statistics for the absolute values and the change from Baseline values by treatment. The change from Baseline values for weight and BMI will also be analyzed by nonparametric rank ANCOVA to compare between the SEP-363856 and placebo treatments.

15.3.6.5. Physical/Neurological Examination

All physical and neurological exam findings at screening will be captured in the medical history and summarized together with the other medical history events. Clinically significant changes from the screening visit will be captured as AEs as appropriate, and summarized together with the other AEs.

15.3.6.6. Concomitant Medications

All medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical) classification (i.e. ATC level 3) and preferred name using the World Health Organization Drug Dictionary (WHO-DD).

Any medications taken during the course of the study, with a start date on or after the date of the first dose of study drug and on or before the date of the last dose of study drug; or with a start date prior to, and an end date on or after, the date of the first dose of study drug, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the date of the first dose of study drug will be considered prior medications. Medications that started after the date of the last dose of study drug will not be considered concomitant, but will be considered post-treatment. Prior and Concomitant medications will be summarized for the number and

percentage of subjects using each medication by treatment and by the drug class and preferred name for the safety population.

15.3.6.7. Suicidality Measure

Frequency and severity of suicidal ideation and suicidal behavior as measured by the C-SSRS scale will be summarized by treatment for each visit.

15.3.6.8. Movement Disorder Measures

Movement disorder measures include AIMS, BARS, and SAS. Change from baseline at Week 4 in the total score of AIMS, BARS, or SAS will be analyzed using an MMRM model similar to that described in the primary analysis for the primary efficacy endpoint (Section 15.3.5.1), with the respective baseline values as covariate.

In addition, as a supportive analysis, missing AIMS (or BARS, SAS) data at the Week 4 visit will be imputed using the LOCF method. The resulting efficacy variable will be the change from baseline in AIMS (or BARS, SAS) total score at the Week 4 LOCF endpoint. This variable will be analyzed using an ANCOVA model similar to that described in Section 15.3.5.2, with the respective baseline values as covariate.

15.3.6.9. Drug Effects Questionnaire

Data from the DEQ questionnaire will be summarized for the safety population by treatment at each visit.

15.3.6.10. Pittsburgh Sleep Quality Index

Data from the PSQI scale will be summarized for the safety population by treatment at each visit. Change from baseline in the PSQI global score at Week 4 will be analyzed using an ANCOVA model similar to that described in Section 15.3.5.3).

15.3.6.11. Subgroup Analysis

Selected safety data will be presented by geographic region/country or by gender subgroups. Details of subgroup analysis of the safety data will be provided in SAP.

15.3.7. Population Pharmacokinetic Analysis

All concentrations will be presented in data listings. POP PK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately.

15.3.8. Pharmacodynamic Analysis

The relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods will be explored, the results of which will be reported separately.

15.3.9. Pharmacogenomic Analysis

The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on plasma SEP-363856 exposure will be explored; the results of which will be reported separately.

15.3.10. Interim Analysis

No interim analysis is planned.

15.3.11. Treatment of Missing Data

For rating scales with more than one item, such as PANSS and MADRS, if any item score contributing to the total/subscale score is missing, then the total/subscale score will be set to missing.

Missing data at the Week 4 visit will be imputed using the last observation carried forward (LOCF) approach for the ANCOVA models, where specified. For the MMRM models, no imputation for missing data will be applied unless otherwise specified.

15.3.12. Sensitivity Analyses

This section describes the sensitivity analyses for the efficacy data.

As a supportive analysis for the efficacy endpoints of change from Baseline in PANSS total score or CGI-S score at Week 4, missing data at Week 4 in PANSS total score and CGI-S score will be imputed using the LOCF method, and the data will be analyzed using an ANCOVA model. The respective response variable for the model will be: change from Baseline in PANSS total score at the Week 4 LOCF endpoint and change from Baseline in CGI-S score at the Week 4 LOCF endpoint. The ANCOVA model will include treatment and pooled center as fixed factors and include Baseline PANSS total score (or CGI-S score) as a covariate.

Subjects will be grouped by the visit at which they had their last PANSS total score (or CGI-S score) measured. This will result in six categories of subject discontinuation: Day 4 dropouts, Week 1 dropouts, Week 2 dropouts, Week 3 dropouts, Week 4 dropouts, and Completers. Mean change from Baseline in PANSS total score and mean change from Baseline in CGI-S score will be plotted by the dropout category and by reason of discontinuation, in order to assess whether these two efficacy measures appear to be correlated with study dropout.

The mechanisms that cause missing data may or may not be at random. The MMRM model used in the primary analysis of the two efficacy endpoints above relies on the assumption of missing at random (MAR). In order to explore the robustness of the primary analyses, sensitivity analyses, such as a random effects pattern mixture model and a pattern mixture model with placebo-based multiple imputation, will be performed for these two efficacy endpoints. Details of these analyses will be provided in the SAP.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL /DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results) will be recorded in the subject's electronic CRF. Data will be entered into source documents prior to being transcribed into the CRF. This transcribing will be done once a subject has passed screening (Visit 1). Data for screen failures will not be collected. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulations (CFR) Part 11. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator or delegate.

16.2. Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 8: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent	A
Review inclusion/exclusion criteria	A
Demographics	A
Prior/concomitant medication review	A
Randomize (IXRS) to treatment	E
Dispense study drug	A, E
Study drug accountability	A
Medical history	A
Psychiatric history/mental status	A
SCID-CT	A
Physical examination	A
Height	A
Vital sign measurements	A
Weight	A
Waist circumference	A
Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B

Table 8: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Serum prolactin	B
Glycosylated hemoglobin (HbA1c)	B
Glucose and Lipid panel	B
Serum follicle stimulating hormone (FSH)	B
Serum human chorionic gonadotropin (β-hCG)	B
Blood sample for pharmacogenomics (CYPP450 2D6)	D
Blood sample for SEP-363856 PK	D
Urine drug screen	B
Urine β-hCG (local)	A
Urine drug screen (central)	B
Positive and Negative Syndrome Scale (PANSS) – Total Score	F
Clinical Global Impression – Severity (CGI-S)	F
Montgomery-Asberg Depression Rating Scale (MADRS)	F
Columbia Suicide Severity Rating Scale (C-SSRS)	F
Drug Effects Questionnaire (DEQ)	A
Abnormal Involuntary Movement Scale (AIMS)	F
Barnes Akathisia Rating Scale (BARS)	F
Simpson-Angus Scale (SAS)	F
Brief Negative Symptoms Scale (BNSS)	F
Pittsburg Sleep Quality Index (PSQI)	F
CogState Brief Battery (CBB)	G
Pretreatment event monitoring	A
Adverse events (AE) monitoring	A
Provide meals	A
Statistical analysis	SAS®, version 9.2 or higher

A = EDC (MediData RAVE); B = LIMS; C = Core Lab Over-read; D = LIMS/ASCII; E = IXRS; F = Bracket; G = CogState.
Abbreviations: EDC = electronic data capture; CDR = clinical data repository; CIMS = Clinical Inventory Management System; IXRS = interactive response technology; IVRS = interactive voice recognition system; LIMS = laboratory information management system.

16.3. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with ICH GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.4. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of centre facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/centre SOPs, protocol, ICH GCP and local regulations. The Investigator or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the IEC. Should the Investigator or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

16.5. Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.6. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis for most of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director's curricula vitae and a current, dated copy of normal range values.

A local laboratory may optionally be used for analysis of serum pregnancy at Visit 2 in this study. The local laboratory/site personnel will provide Sponsor/P1vital with laboratory certification(s) and a current dated copy of normal range values for the local clinical laboratory selected to analyse clinical specimens.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the “Investigator Approval" page.

17.2. Institutional Review Board/Independent Ethics Committee

Documented approval for conducting the study from appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB/IEC chairman or designee identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB/IEC complies with the requirements in 21 CFR Part 56 for a study conducted under a US investigation new drug (IND) or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. All informed consent forms must contain the minimum elements as mandated by ICH

GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study drug, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject, and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent form must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm uphold the subjects confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

If any cases are identified where the subject's confidentiality has been breached, this must be rectified immediately. All subject identifiable information should be removed and the Sponsor notified.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately/within five business days of the occurrence, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 25 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

The Sponsor will disclose the study results, in the form of a clinical study report synopsis, to the IEC and the applicable regulatory authorities within one year of the end of the study. The format of this synopsis and that of the clinical study report should comply with ICH E3 guidelines for structure and content of a clinical study report.

Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

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19. INVESTIGATOR APPROVAL

I have read the protocol, SEP361-201, Version 3.01 "A 4-Week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexibly-dosed, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Adult Subjects With Schizophrenia", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

Electrocardiogram (ECG) equipment and supplies will be provided by the centralized cardiac safety vendor and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested 10 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the study center for review and signature.
- The ECG tracing will be kept with subject's source documentation and / or CRF unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the study center.

4. Data Standardization

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

21. APPENDIX II. HIGHLY EFFECTIVE CONTRACEPTIVE PROCEDURES FOR AND DURING THE STUDY

For female subjects

Female subject of reproductive potential agrees to remain abstinent or use highly effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken. In the Investigator's judgment, the subject will adhere to this requirement.

a. Highly effective contraception is defined as continuous use of either two barrier methods (eg, condom and spermicide or diaphragm with spermicide) or a hormonal contraceptive. Highly effective hormonal contraceptives include the following:

   i) contraceptive implant (such as Norplant®) implanted at least 90 days prior to screening;

   ii) injectable contraception (such as medroxyprogesterone acetate injection) given at least 14 days prior to screening; or

   iii) oral contraception taken as directed for at least 30 days prior to screening.

b. Subjects who are of non-reproductive potential, ie, subject who is surgically sterile, has undergone tubal ligation, or is postmenopausal (defined as at least 12 months of spontaneous amenorrhea or between 6 and 12 months of spontaneous amenorrhea with follicle stimulating hormone (FSH) concentrations within postmenopausal range as determined by laboratory analysis) are not required to remain abstinent or use highly effective contraception**.**

For Male Subjects

Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use highly effective methods of birth control from screening until at least 30 days after the last study drug administration. Male subjects must be surgically sterile or willing to use an effective method of double-barrier birth control as outlined for female subjects above.

22. APPENDIX III. HALOPERIDOL EQUIVALENT DOSES

Medications	Haloperidol Equivalent (12 mg)
Typical Antipsychotics[a]	
Chlorpromazine	600 mg
Fluphenazine	15 mg
Haloperidol	12 mg
Perphenazine	40 mg
Thioridazine	500 mg
Thiothixene	30 mg
Trifluoperazine	25 mg
Fluphenazine decanoate (mg/2–3 wk)	34 mg/2-3 wk
Haloperidol decanoate (mg/4 wk)	159 mg/4 wk

Medications	Haloperidol Equivalent (12 mg)
Atypical Antipsychotics[a]	
Aripiprazole	30
Asenapine	30
Clozapine	900
Haloperidol	12
Iloperidone	24
Lurasidone	120
Olanzapine	20
Paliperidone	9
Quetiapine	450
Risperidone	6
Sertindole	36
Ziprasidone	160

a. Antipsychotics: The tables are provided for guidance purposes only. Dose range allowed must be determined for the region after consultation with the medical monitor.

References:

Gardner DM, Murphy AL, O'Donnell HO, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. Am J Psychiatry 2010;167:686-693.

Leucht S, Samara M, Patel M, Woods S, and Davis J. Dose Equivalents for Second-Generation antipsychotics: The Minimum Effective Dose Method. Schizophr Bull. 2014 Feb;40 (2):314-326.

Stahl SM. A pocket guide to atypical antipsychotics: dosing, switching, and other practical information. Arbor Scientia; 2013.

23. APPENDIX IV. CLINICAL LABORATORY TESTS

Detailed instructions will be provided in a study center manual.
The following clinical laboratory tests are to be performed:

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)
Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Creatine phosphokinase (CPK), Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Prolactin, Protein (Total), Sodium (Na), Uric Acid

URINALYSIS: Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

LIPID PANEL: LDL-Cholesterol, HDL-Cholesterol, Triglycerides

THYROID PANEL: Free T3, Free T4, Thyroid stimulating hormone (TSH)

URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

OTHER TESTS: Serum Pregnancy (β-HcG) (in female subjects only), Urine Pregnancy Test (in female subjects only), Glycosylated hemoglobin (HbA_{1c})

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

24. APPENDIX V. PHARMACOKINETIC SAMPLING AND SAMPLE HANDLING GUIDELINE

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

BLOOD SAMPLES FOR PLASMA PHARMACOKINETICS

When blood sample for PK assessment and clinical lab sample collections share the same designated time points (including predose sample), the blood samples should be collected during the same venipuncture.

For each defined PK sampling time point, collect 6 mL blood sample into a K2-EDTA treated tube. Invert gently 8 to 10 times. Keep the blood collection tube on wet ice upon blood draw, and centrifuge for 20 minutes at ca. x 1300 g to isolate plasma within 30 minutes of blood draw. To ensure a more homogenous sample, all plasma samples should first be transferred to 1 tube, capped and mixed well. Split the harvest plasma sample with approximately equal volume into 2 polypropylene tubes, and label as Primary and Back-up. Freeze plasma tubes in a freezer set at approximately -20°C or lower. The date and clock time of blood collection must be recorded.

Blood must be collected from all subjects at the time points indicated below.

All samples will be shipped with sufficient dry ice protection.

Study Day	Collection Time	Volume Collected
Day 1	Pre-dose (approximately 10 minutes prior to dosing)	6 mL
Day 29	Post-dose (Actual date and clock time will be recorded)	6 mL

25. APPENDIX VI. SAMPLE COLLECTION AND HANDLING GUIDELINES FOR PHARMACOGENOMICS ASSESSMENT

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

BLOOD SAMPLES FOR PHARMACOGENOMICS

- A blood sample (approximately 4.0 mL) will be collected predose on Day 1 using a 4-mL Vacutainer® (or equivalent) collection tube containing K2-EDTA as an anticoagulant.
- The tubes containing blood samples will be labeled with the following information: unique barcode (if possible), protocol number, subject number, and sample date of collection.
- Blood samples will be kept upright on wet ice upon blood draw and will be stored frozen at approximately -70°C within 10 min of collection until shipment to the appropriate laboratory.
- The blood samples for pharmacogenomics will be shipped in leak-proof double-plastic sealed bags with approximately 20 pounds of dry ice placed in insulated shipping containers labeled on the outside with “Human Specimens/Non-infectious”. Packing material such as bubble-wrap or other cushioning material will be placed around the samples to prevent breakage during shipping. Samples will be shipped in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.
- Samples will be shipped via Sponsor-specified overnight courier service on Monday through Wednesday (should be shipped at least 2 days prior to National Holiday)

26. APPENDIX VII. MINIMUM PANSS TOTAL SCORE CRITERIA AT BASELINE

The following formula is to be utilized to determine the PANSS total score change at Baseline (Visit 2):

$$\frac{\text{PANSS total score at Screening - PANSS total score at Baseline}}{\text{PANSS total score at Screening - 30}} \times 100\%$$

PANSS total score at Screening (V1)	MINIMUM Permissible PANSS total score at Baseline (V2)
80	80
81	80
82	80
83	80
84	80
85	80
86	80
87	80
88	80
89	80
90	80
91	80
92	80
93	81
94	82
95	83
96	83
97	84
98	85
99	86
100	87
101	87
102	88

PANSS total score at Screening (V1)	MINIMUM Permissible PANSS total score at Baseline (V2)
103	89
104	90
105	91
106	91
107	92
108	93
109	94
110	95
111	95
112	96
113	97
114	98
115	99
116	99
117	100
118	101
119	102
120	103
121	103
122	104
123	105
124	106
125	107
126	107
127	108
128	109
129	110
130	111