SEP-363856

Clinical Study Protocol SEP361-304

A Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Long-term Safety and Tolerability of SEP-363856 in Subjects with Schizophrenia

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	PPD , MD PPD Sunovion Pharmaceuticals, Inc.	Telephone: PPD Email: PPD
Medical Monitor	PPD MD, Psych, PhD PPD Central Nervous System Medical and Scientific Services Data Sciences, Safety and Regulatory IQVIA	PPD Office: PPD Mobile: PPD Email: PPD
24-Hour Urgent Medical Contact	IQVIA Medical Emergency Contact Center	US: CCI or CCI Europe: CCI
SAE/Pregnancy Reporting	PPD Pharmacovigilance (PVG)	Hotline Number: CCI Fax (US): CCI Fax (Europe): CCI Email: CCI

1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: SEP-363856

Title of Study: A Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Long-term Safety and Tolerability of SEP-363856 in Subjects with Schizophrenia

Proposed Indication: Schizophrenia

Study Centers: Approximately 50 global study centers

Phase of Development: 3

Study Objectives:

Primary Objective:

To evaluate the long-term safety and tolerability of flexibly-dosed SEP-363856 (50, 75, and 100 mg/day) in clinically stable adult subjects with chronic schizophrenia based on safety parameters, including the incidence of overall adverse events (AEs), serious AEs (SAEs) and AEs leading to discontinuation.

Other Safety Objectives:

- To evaluate the long-term safety and tolerability of SEP-363856 by assessing:
  - physical examinations (PE)
  - 12-lead electrocardiograms (ECG)
  - vital sign measurements
  - clinical laboratory tests
  - suicidality using the Columbia – Suicide Severity Rating Scale (C-SSRS)
  - movement disorder abnormalities using the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS)
- To evaluate the effects of SEP-363856 (50 to 100 mg/day) on prolactin, HbA1c, lipids, and glucose concentrations, body weight, and body mass index (BMI) compared to quetiapine XR (400 to 800 mg/day)
- To evaluate the impact of SEP-363856 on healthcare resource utilization

Other Efficacy Objectives:

- To evaluate the long-term effectiveness of SEP-363856 and quetiapine XR using the
  - Positive and Negative Syndrome Scale (PANSS)
  - Clinical Global Impression-Severity (CGI-S) scale
  - Brief Negative Symptom Scale (BNSS)
  - Montgomery-Asberg Depression Rating Scale (MADRS)
- To evaluate the maintenance efficacy of SEP-363856 and quetiapine XR (including time to relapse, rate of relapse and frequency of hospitalization due to relapse)
- To evaluate adherence to study treatment based on time to all cause discontinuation

- To evaluate the effects of SEP-363856 and quetiapine XR on daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS)
- To assess the effects of SEP-363856 and quetiapine XR on cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS)
- To explore the effects of SEP-363856 and quetiapine XR on functional capacity as measured by the University of California San Diego (UCSD) Performance-Based Skills Assessment – Brief Version (UPSA-B)
- To evaluate the effects of SEP-363856 and quetiapine XR on function as measured by the modified Specific Level of Functioning Scale (SLOF)
- To evaluate the effects of SEP-363856 and quetiapine XR on health-related quality of life as measured by the EuroQol-5D-5L (EQ-5D-5L)
- To evaluate medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ)
- To explore the impact of SEP-363856 on nicotine use

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Study Design:

This is a 52-week, multicenter, randomized, double-blind, parallel-group, flexible-dose study designed to evaluate the long-term safety and tolerability of SEP-363856 (50 to 100 mg/day) in clinically stable adults with schizophrenia. This study is projected to randomize approximately 300 subjects to two treatment groups (SEP-363856 50 to 100 mg/day or quetiapine XR 400 to 800 mg/day) in a 2:1 ratio. Study drug will be taken at the same time each evening at bedtime and should be taken without food or with a light meal.

A Data and Safety Monitoring Board (DSMB) will review safety data approximately every 6 months during the study. The DSMB will be independent of the Sponsor, study contract research organization (CRO) and the Investigators and will be empowered to recommend stopping the study due to safety concerns. The membership of the DSMB and its mandate will be described in a separate DSMB Charter.

The study will consist of three periods: Screening/Washout (up to 21 days), Treatment (52 weeks) and a Follow-up visit (7 days after the last study drug dose).

Screening/Washout Period (up to 21 days):

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a Screening/Washout Period of up to 21 days, during which they will be tapered off all psychotropic medications (except as noted in the Concomitant Medications section below) in a manner that is consistent with labeling recommendations and conventional medical practice. The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

Subjects may be hospitalized for up to one week prior to randomization during the Screening/Washout Period, if deemed clinically necessary by the Investigator. Additional hospitalization during the

Screening/Washout Period beyond one week may be allowed after approval from the Medical Monitor.

Subjects who screen fail may be re-screened once, if judged appropriate by the Investigator after discussion with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

Double-Blind Treatment Period (52 weeks):

At Baseline (Day 1), subjects who have successfully completed the washout of psychotropic medications and have met the eligibility criteria will be randomly assigned via interactive web response system (IWRS) to SEP-363856 or quetiapine XR treatment groups in a 2:1 ratio. Study drug dosing will begin the evening of the Baseline visit. Treatment will continue once-daily, in the evening at bedtime, for the remainder of the Treatment Period, during which the procedures outlined in Table 2 will be conducted. Subjects will be seen at Baseline, Weeks 1, 2 and 4, and then every 4 weeks thereafter up to Week 52. Telephone calls will be made by a member of the clinical research staff to the subject weekly between visits that are more than one week apart to collect AEs and concomitant medications, as well as to remind the subject about adherence to study drug administration and upcoming visits.

Subjects may be hospitalized for the first 7 days of the Treatment Period, if deemed clinically necessary by the Investigator. Further hospitalization during the Treatment Period will require approval from the Medical Monitor.

Subjects randomized to the SEP-363856 group will receive SEP-363856 50 mg/day from Day 1 through Day 3 and 75 mg/day from Day 4 through Day 7. Beginning on Day 8, the dose can be adjusted among 3 dose levels (50, 75, and 100 mg/day), as deemed clinically appropriate by the Investigator.

Subjects randomized to the quetiapine XR group will receive quetiapine XR 300 mg/day on Days 1 and 2, 400 mg/day on Days 3 and 4 and 600 mg/day from Day 5 through Day 7. Beginning on Day 8, the dose can be adjusted among 3 dose levels (400, 600, and 800 mg/day), as deemed clinically appropriate by the Investigator.

Dose adjustments made to either SEP-363856 or quetiapine XR will be done in a blinded fashion. Dose increases can be made no more frequently than weekly to the next higher dose level beginning on Day 8, if the response to the previous dose level is not adequate and there are no significant tolerability problems, based on Investigator judgement. Increases in dose will occur at regularly scheduled study visits when possible. However, dose increases between regularly scheduled visits may occur (as long as the subject has been taking the previous dose level for at least 7 days). If a dose increase is performed between regularly scheduled visits, subjects will be required to return to the clinic at an unscheduled visit for drug dispensation.

Dose reductions can be made to the next lower dose level at any time (at least 1 day apart) beginning on Day 8 for tolerability issues as judged by the Investigator. If a dose reduction is needed between study visits, subjects will be asked to return to the clinic for an unscheduled visit for drug dispensation.

For subjects who have received study drug and who prematurely discontinue from the study treatment, every effort should be made to complete the final evaluation procedures within 48 hours of the last study drug dose at the early termination (ET) visit.

Follow-up Period (1 week):

Subjects who discontinue early from the study or complete the study will be required to complete the Follow-up Visit 7 days (± 2 days) post last dose of study drug.

Number of Subjects (planned): 300 subjects

Diagnosis and Criteria for Subject Inclusion:

Inclusion criteria:

The main inclusion criteria include, but are not limited to the following:

- Male or female subject between 18 to 65 years of age (inclusive) at the time of consent.
- Subject meets DSM-5 criteria for a diagnosis of schizophrenia as established by clinical interview at Screening (using the DSM-5 as a reference and confirmed using the SCID-CT). The time since the subject's diagnosis must be ≥ 1 year prior to Screening.
- Subject must have a CGI-S score ≤ 4 at Screening and Baseline.
- Subject must have a PANSS total score ≤ 80 at Screening and Baseline.
- Subject is judged to be clinically stable (i.e., no evidence of an acute exacerbation) by the Investigator for at least 8 weeks prior to Screening.
- Subject has had no change in antipsychotic medication(s) (minor dose adjustments for tolerability purposes are permitted) for at least 6 weeks prior to Screening.
- Subjects taking an antipsychotic agent at Screening may participate in this study only if there are signs of intolerability or lack of efficacy of the current antipsychotic (as determined by the Investigator).
- Subject is, in the opinion of the Investigator, generally healthy based on Screening medical history, PE, neurological examination, vital signs, electrocardiogram (ECG) and clinical laboratory values (hematology, chemistry and urinalysis).

Exclusion criteria:

Main exclusion criteria include, but are not limited to:

- Subject was hospitalized for a psychiatric illness within the 8 weeks prior to Screening.
- Subject has a current DSM-5 diagnosis or presence of symptoms consistent with a DSM-5 diagnosis other than schizophrenia. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months or for a total of ≥ 10 years during the subject's lifetime), substance (other than nicotine or caffeine) use disorder within past 12 months or for a total of ≥ 10 years during the subject's lifetime, major depressive disorder, schizoaffective disorder, bipolar I or II disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms are not the primary focus of treatment.
- Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents within a 1-year period prior to Screening, given at adequate dose as per labeling, for at least 4 weeks.
- 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 Screening (i.e., in the past one month) or at Baseline (i.e., since last visit).
- Subject is at significant risk of harming self or others based on Investigator's judgment.
- Subject has attempted suicide within 6 months prior to Screening.
- Subject has received treatment with a psychotropic medication or herbal supplement within 3 days or 5 half-lives (whichever is longer) prior to randomization or anticipates

the need for psychotropic medications or herbal supplements during their participation in this study, with the exception of the medications specified in the Concomitant Medications section of this document. The following medications have additional washout requirements as specified below:

- Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to randomization.
- Fluoxetine must be discontinued at least 28 days prior to randomization.
- Clozapine used at 200 mg/day or less for insomnia, agitation or anxiety must be discontinued at least 28 days prior to randomization. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation.
- Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to randomization.

- Subject has received electroconvulsive therapy (ECT) treatment within the 3 months prior to Screening or is expected to require ECT during the study.
- Subject has been treated with quetiapine or quetiapine XR within the 6 weeks prior to Screening or has a history of inadequate response or intolerability to quetiapine or quetiapine XR.
- 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.
- Subject has any clinically significant abnormal laboratory value(s) at Screening.

Investigational Product, Dosage and Mode of Administration:

SEP-363856 over-encapsulated tablets (50 mg, 75 mg or 100 mg) will be utilized. Study drug will be administered orally once daily. Study drug will be taken at the same time each evening at bedtime and may be taken without food or with a light meal.

Subjects randomized to SEP-363856 will receive SEP-363856 50 mg/day from Day 1 through Day 3 and 75 mg/day from Day 4 through Day 7. Beginning on Day 8, the SEP-363856 dose can be adjusted within the range of 50 mg/day to 100 mg/day in 25 mg increments (i.e. 50, 75, or 100 mg/day). Dose increases are to be made no more frequently than weekly. Dose reductions for tolerability issues as judged by the Investigator can be made at intervals as short as 1 day.

Duration of Treatment: 52 weeks

Reference Therapy, Dosage and Mode of Administration:

Quetiapine XR matching over-encapsulated tablets (300 mg and 400 mg) will be utilized. Study drug will be administered orally once daily. Study drug will be taken at the same time each evening at bedtime and may be taken without food or with a light meal.

Subjects randomized to quetiapine XR will receive quetiapine XR 300 mg/day on Days 1 and 2, 400 mg/day on Days 3 and 4, and 600 mg/day from Day 5 through Day 7. Beginning on Day 8, the quetiapine XR dose can be adjusted within the range of 400 mg/day to 800 mg/day in 200 mg increments (400, 600, or 800 mg/day). Dose increases are to be made no more frequently than weekly. Dose reductions for tolerability issues as judged by the Investigator can be made at intervals as short as 1 day.

Concomitant Medications:

Prior Medications:

Treatment with oral psychotropic medications and any other medications with a propensity for psychotropic effects (with the exception of the medications described below under Allowed Concomitant Psychotropic Medications) must be discontinued at least 3 days or 5 half-lives (whichever is longer) prior to randomization in a manner that is consistent with labeling recommendations and conventional medical practice.

The following psychotropic medications have additional washout requirements:

- MAO inhibitors must be discontinued at least 28 days prior to randomization.
- Fluoxetine must be discontinued at least 28 days prior to randomization.
- Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to randomization. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for an indication other than insomnia, agitation, or anxiety are excluded from study participation.
- Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to the randomization visit.

Treatment with the sedative hypnotics described below under Allowed Concomitant Psychotropic Medications is permitted during the Screening/Washout Period but should be tapered as clinically appropriate to conform with and adequately prepare the subject for the protocol-specified limitations applicable to these agents following randomization. Subjects should not be taken off their current effective medications for treatment of schizophrenia for purposes of participating in this study.

Treatment with medications used to treat movement disorders must be discontinued at least 1 day prior to randomization.

Prohibited Medications:

Psychotropic medications and medications with a propensity for psychotropic effects are not permitted during the Treatment Period, except for the medications discussed below under Allowed Concomitant Psychotropic Medications. The use of psychotropic medications is permitted after the last dose of study medication provided they are not administered prior to the final PANSS assessment.

The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications are not permitted during the Treatment Period; however, they are permitted after the last dose of study medication provided they are not administered prior to the final PANSS assessment.

Subjects who are administered a psychotropic medication (other than the study drug and the acceptable medications described below under Allowed Concomitant Psychotropic Medications) for the purposes of treating an exacerbation of symptoms associated schizophrenia or due to lack of efficacy of the study treatment will be discontinued from the study.

Allowed Concomitant Psychotropic Medications:

Treatment with benztropine (benzotropine outside the United States [US]) up to 6 mg/day is permitted, as needed, for motor symptoms. 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) is permitted as needed for akathisia. These allowed medications for the treatment of EPS and akathisia may be given in any formulation (oral, intramuscular [IM] or intravenous [IV]) as deemed appropriate by the Investigator. Medications used to treat motor

symptoms should not be given prophylactically. They are to be tapered and discontinued 1 day prior to randomization but may be reinstated if symptoms emerge post-randomization during the study.

Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem, zolpidem controlled release (CR), diphenhydramine, and melatonin is permitted at the discretion of the Investigator with the following restrictions:

- Oral 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.
- Diphenhydramine ≤ 100 mg/day and melatonin ≤ 5 mg/day may be administered at bedtime for insomnia, as needed. Over-the-counter melatonin should be used. Combination melatonin products are not allowed.
- temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, as needed.
- Medications that are used for insomnia should be administered no more than once nightly and should not be used in combination.
- Medications used for the treatment of anxiety/agitation and insomnia (e.g., 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 above specified drugs available, similar drugs at equivalent dosages will be permitted in consultation with the Medical Monitor.

The date and 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 any psychotropic medication (or any agents that may cause sedation) within 8 hours of efficacy assessments.

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

Concomitant Non-psychotropic Medications:

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% total daily dose) for at least 30 days prior to screening. The dose for the concomitant medication may change, as needed, after randomization (or be discontinued). This includes β-adrenergic antagonists used to treat stable hypertension. Routine vaccines (i.e., seasonal influenza, pneumonia, etc.) are allowed based on the investigator's judgment. Female subjects may use contraception as detailed in Section 10.5.

In addition, use of non-prescription pain medications (e.g., aspirin, acetaminophen/paracetamol, ibuprofen) are allowed during the study provided these medications do not have a propensity for psychotropic effects.

The Medical Monitor should be consulted, if possible, before administering medications for short-term treatment of an acute medical condition. If medications are administered for short-term treatment of an acute medical condition without prior consultation with the Medical Monitor, the Medical Monitor is to be informed of such medication use as soon as possible and the appropriateness for the subject to continue in the study should be discussed with the Medical Monitor.

Study Endpoints:

Primary Endpoint:

- The incidence of overall AEs, SAEs, and AEs leading to discontinuation

Other Safety Endpoints:

- Observed values and changes from Baseline in clinical laboratory tests (hematology, chemistry and urinalysis)
- 12-lead ECG (including heart rate, RR, PR, QRS, QT, QTc-F and QTc-B)
- Observed values and changes from Baseline in vital signs (including body weight, BMI, waist circumference, temperature, blood pressure [supine and standing], heart rate [supine and standing] and respiratory rate)
- Frequency and severity of suicidal ideation and suicidal behavior based on the C-SSRS
- Changes from Baseline in BARS, AIMS and SAS scores
- Healthcare resource utilization (HRU) (including numbers of physician office visits, ER visits and hospitalizations, length of hospital stays, employment status and average number of hours caregiver spends helping subjects per week).

Other Efficacy Endpoints:

- Changes from Baseline in:
  - PANSS total score and subscale scores (positive, negative, and general psychopathology)
  - CGI-S score
  - BNSS total score
  - MADRS total score
  - ESS total score
  - BACS composite score
  - UPSA-B total score
  - SLOF total and subscale scores
  - EQ-5D-5L visual analog scale (VAS), index score and dimension score
  - MSQ score
- Time to relapse, rate of relapse, and frequency of hospitalization due to relapse. Relapse will be defined as the earliest occurrence of any of the following:
  - Worsening of > 30% PANSS total score from Baseline and CGI-S > 3
  - Hospitalization for worsening of psychosis
  - Emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others
  - Discontinuation from the study due to exacerbation of the underlying illness of schizophrenia
- Time to all cause discontinuation from the study
- Change from Baseline in tobacco use
- Plasma cotinine concentrations

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Statistical Methods:

The analysis of the long-term safety and tolerability, and efficacy will be based on the safety population, which includes all subjects who receive at least one dose of study drug during the 52-week Treatment Period. Analysis results will be presented for each treatment separately.

The primary objective of this study is to assess the safety and tolerability of SEP-363856 treatment for up to 52 weeks of double-blind treatment in clinically stable outpatients with chronic schizophrenia.

AEs, 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 up to 9 days following the last dose of study drug. All AEs starting after the last dose of study drug up to 9 days following the last dose will be summarized separately.

Observed values and changes from Baseline in clinical laboratory tests (hematology, chemistry and urinalysis), vital sign parameters (temperature, body weight, BMI, waist circumference, blood pressure [supine and standing], heart rate [supine and standing], and respiratory rate) and 12-lead ECG parameters will be summarized descriptively by treatment group. The frequency and severity of suicidal ideation and suicidal behavior based on the C-SSRS will be provided.

A nonparametric rank analysis of covariance (ANCOVA) will be applied to Week 52 prolactin, HbA_{1c}, lipids, and glucose levels, as well as body weight and BMI in order to compare changes from Baseline values between treatment groups with adjustments for Baseline value.

Movement disorder abnormalities will be assessed using the SAS, BARS, and AIMS scales. Mean changes from Baseline in these measures by scheduled visit will be presented.

HCRU responses will be summarized descriptively.

Descriptive statistics will be presented on the change from Baseline in PANSS total and subscale scores, CGI-S score, BNSS total score, MADRS total score, ESS total score, BACS composite score, SLOF total and subscale scores, EQ-5D-5L scores, UPSA-B total score and MSQ score. The proportion of subjects who achieve a response, defined as a 20% or greater improvement in PANSS total score from Baseline will be calculated. Time to relapse and time to all cause discontinuation will be analyzed with Kaplan-Meier methods.

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Sample Size:

A total of 300 subjects are expected to be enrolled from approximately 50 global sites, including the US and Europe. Subjects will be assigned randomly to receive SEP-363856 or active comparator in an allocation ratio of 2:1. The determination of sample size was based upon clinical considerations. The sample size of 300 subjects will provide approximately 80 subjects who are expected to complete 1 year of treatment with SEP-363856 to support sufficient long-term safety data on SEP-363856.

Table 2: Schedule of Assessments

Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 (EOT/ ET)[a]**	**18**
Study Week	**Screening/ Washout[b]**	**Baseline[c]**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Follow-up[d]**
Study Day[e]	**-21 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**7±2 d after last dose**
Obtain informed consent	X																	
CCI																		
Review inclusion/exclusion criteria	X	X																
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize (IWRS) to treatment		X																
Dispense study drug[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demography	X																	
Medical history	X																	
Psychiatric history	X																	
Tobacco use information		X					X			X							X	
SCID-CT[g]	X																	
Telephone contacts[h]			Telephone calls to the subjects will be made at Weeks 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27, 29, 30, 31, 33, 34, 35, 37, 38, 39, 41, 42, 43, 45, 46, 47, 49, 50, and 51. Unscheduled visits may occur at the discretion of the Investigator.													

Table 2: Schedule of Assessments (Continued)

Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 (EOT/ ET)[a]**	**18**
Study Week	**Screening/ Washout[b]**	**Baseline[c]**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Follow-up[d]**
Study Day[e]	**-21 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**7±2 d after last dose**
Physical and neurological examinations	X				X		X			X			X				X	X
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (including BMI[j])	X	X			X		X			X			X				X	
Height	X																	
Waist circumference		X			X		X			X			X				X	
12-Lead ECG	X	X	X		X		X			X			X				X	
Hematology, chemistry, urinalysis[k]	X	X	X		X		X			X			X				X	
Blood sample for hepatitis screening	X																	
Serum FSH[l]	X																	
Serum β-hCG, females of childbearing potential	X																	
CCI																		
CCI																		
Plasma cotinine level[o]		X					X			X							X	

Table 2: Schedule of Assessments (Continued)

Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 (EOT/ ET)[a]**	**18**
Study Week	**Screening/ Washout[b]**	**Baseline[c]**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Follow-up[d]**
Study Day[e]	**-21 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**7±2 d after last dose**
Urine drug screen[p]	X	X	X		X		X			X			X				X	
Urine β-hCG, females only[q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PANSS[v]	X	X	X		X	X		X		X		X		X		X	X	
BNSS		X	X		X	X		X		X		X		X		X	X	
MADRS		X	X		X	X		X		X		X		X		X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X		X	X		X		X		X		X		X	X	
SAS[r]		X	X		X					X							X	
BARS[r]		X	X		X					X							X	
AIMS[r]		X	X		X					X							X	
EQ-5D-5L		X															X	
ESS		X								X							X	
BACS		X					X			X							X	
UPSA-B		X					X			X							X	
SLOF		X					X			X							X	
MSQ	X[s]																X	
Healthcare resource Utilization		X					X			X			X				X	

Table 2: Schedule of Assessments (Continued)

Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 (EOT/ ET)[a]**	**18**
Study Week	**Screening/ Washout[b]**	**Baseline[c]**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Follow-up[d]**
Study Day[e]	**-21 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**7±2 d after last dose**
Pretreatment / AE monitoring[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Duplicate subject check[u]	X																	

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition in Schizophrenia; BARS = Barnes Akathisia Rating Scale; β-hCG = human chorionic gonadotropin; BMI = Body Mass Index; BNSS = Brief Negative Symptom Scale; CGI-S = clinical global impression – severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EDC = electronic data capture; EOT = end of treatment; EQ-5D-5L = EuroQual-5D-5L; ESS = Epworth Sleepiness Scale; ET = early termination; FSH = Follicle stimulating hormone; IWRS = interactive web response system; MADRS = Montgomery-Asberg Depression Rating Scale; MSQ = Medication Satisfaction Questionnaire; PANSS = Positive and Negative Syndrome Scale; CCI [redacted]; SAS = Simpson-Angus Scale; SCID-CT = Structured Clinical Interview for DSM-5, Clinical Trials version; SLOF = Modified Specific Level of Functioning scale; UPSA-B = UCSD Performance-Based Skills Assessment – Brief Version; US = United States.

[a] If a subject discontinues from the study, all Early Termination (ET) procedures should be performed at the ET visit, within 48 hours of last study dose.

[b] Subjects who screen fail may be re-screened once after consultation with the Medical Monitor. Screening assessments may occur over multiple days. The Screening Period may be extended for up to 7 days after approval from the Medical Monitor. Subjects may be hospitalized for up to one week prior to randomization during the Screening/Washout Period, if deemed clinically necessary by the investigator. Further hospitalization during Screening/Washout will require approval from the Medical Monitor.

[c] Subjects may be hospitalized for the first 7 days of the Treatment Period, if deemed clinically necessary by the Investigator.

[d] All Subjects will have a safety Follow-up Visit (7 [± 2]) days after their last dose of study drug. While every effort should be made to complete the Follow-up Visit in the clinic, AEs and concomitant medications may be collected by telephone contact if subject is unable to come to the clinic for the Follow-up Visit.

[e] Visit windows are as follows: + 2 days for Visit 3; ± 2 days for Visits 4 and 5; ± 3 days for Visit 6 through Visit 17.

[f] All study drug will be taken once daily in the evening at bedtime by mouth without food or with a light meal.

[g] 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.

[h] Telephone calls will be made by a member of the research staff to the subject between scheduled study visits that are more than one week apart to collect AEs and concomitant medications, as well as to remind subject about adherence to study drug administration and upcoming visits.

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

[j] BMI will be calculated and recorded in the eCRF at the clinical site at Screening. For other visits, BMI will be derived in the EDC system.

[k] Subjects must be fasted (no food or drink except water at least 8 hours prior to specified blood tests). Serum prolactin results will be blinded after the Screening visit. A list of laboratory tests are provided in Section 21.

[l] Blood samples for follicle stimulating hormone (FSH) will be collected for post-menopausal women or if menopause is suspected.

[m] CCI [redacted].

[n] Sample collected at Baseline will be pre-dose. The time and date of the 3 previous doses of study drug prior to blood sampling and the time and date of blood sampling must be recorded. The remaining plasma samples, after PK measurement is completed, CCI [redacted]

[o] Blood samples taken at Baseline and Weeks 12, 24 and 52 for study drug concentration measurement will also be used for the measurement of cotinine levels. No separate blood samples will be collected for cotinine.

[p] Urine drug screen may be ordered at other visits as deemed clinically appropriate. These results should be discussed with the Medical Monitor.

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

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

[s] To be completed at the Screening Visit only for those subjects who were currently treated with an antipsychotic medication.

[t] Events occurring prior to first dose of study drug are programmatically identified as pretreatment events. Events occurring after first dose of study drug are programmatically identified as adverse events.

[u] Duplicate subject check will be performed (where allowed by local/regional regulations). Subject consent is required.

[v] The PANSS-Informant Checklist (PANSS-IC) form will be completed as part of the PANSS.

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definitions 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
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BNSS	Brief Negative Symptom Scale
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression - Severity
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Controlled release
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EDC	Electronic data capture
EOT	End of treatment
EPS	Extrapyramidal symptoms
EQ-5D-5L	EuroQol– 5 Dimensions – 5 Levels
ESS	Epworth Sleepiness Scale
ET	Early termination
FDA	U.S. Food and Drug Administration

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
GCP	Good Clinical Practice
5-HT	5-hydroxytryptamine (serotonin)
HCRU	Healthcare resource utilization
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
IPD	Important protocol deviation
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive 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
MSQ	Medication Satisfaction Questionnaire
MTD	Maximum tolerated dose
NCS	Not clinically significant
PANSS	Positive and Negative Syndrome Scale
PANSS- IC	Positive and Negative Syndrome Scale- Informant Checklist
PD	Pharmacodynamic(s)
PE	Physical examination
PGx	Pharmacogenomic
PK	Pharmacokinetic(s)
PP	Per-Protocol
CCI [redacted]	
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
PVG	Pharmacovigilance

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
QD	Once daily
QRS	Electrocardiographic wave (complex or interval)
QT interval	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RR interval	Distance between two consecutive R waves
SAE	Serious adverse event
SAS	Simpson Angus Scale
SLOF	Specific Level of Functioning Scale
SOC	System organ class
TAAR1	trace amine associated 1 receptors
UCSD	University of California San Diego
UDS	Urine drug screen
US	United States
UPSA-B	UCSD Performance-Based Skills Assessment – Brief Version
VAS	Visual analogue scale
WBC	White blood cells
WHO-DD	World Health Organization - Drug Dictionary

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 randomized.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and active comparator.
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.
Completed Subject	Any subject who participated throughout the duration of the Treatment Period, up to and including Visit 17.
Early Termination	Any subject who was successfully screened and randomized into the Treatment Period of the study but did not complete the Treatment Period of the study.
End of Treatment	The day that the subject receives protocol-defined last dose of the study drug.

4. INTRODUCTION

4.1. Background

Schizophrenia is a chronic and disabling neuropsychiatric 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) (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, atypical agents are associated with 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 (cardiovascular disease, diabetes) 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 before 18 months because of lack of efficacy or occurrence of side effects (Lieberman-2005). Noncompliance often leads to relapse of symptoms and need for rehospitalization (Ascher-Svanum-2010; Munro-2011; Morken-2008). Clearly, an unmet need exists for new, effective, safe and well-tolerated treatments for schizophrenia.

4.2. Study Conduct Rationale

SEP-363856 is a central nervous system (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 therapeutic profile of SEP-363856 has not been completely elucidated but may include actions at 5-HT1A and trace amine associated 1 (TAAR1) receptors.

As of 24 September 2018, a total of 246 subjects have received oral doses of SEP-363856 in 8 completed Phase 1 studies (SEP361-101, SEP361-103, SEP361-104, SEP361-105, SEP361-106, SEP361-108, SEP361-111 and DA801002). An additional 199 subjects received oral doses of SEP-363856 in studies in adults with schizophrenia (Study SEP361-201 and Study SEP361-202) and 24 subjects in an ongoing Phase 1 study (Study DA801004) in Japanese adults with schizophrenia.

Study SEP361-106 was a 2-part, randomized, single-blind, placebo-controlled, ascending multiple oral dose and open label study assessing the safety, tolerability, and pharmacokinetic (PK) profile of SEP-363856 in male and female adults with schizophrenia. Part 1 established the maximum tolerated dose (MTD) for 7 days of multiple dosing of SEP-363856 without titration as 75 mg/day. In Part 2, treatment with SEP-363856 75 mg/day for 28 days demonstrated improvement in efficacy measures (PANSS total score, Clinical Global Impression – Severity [CGI-S]) compared with baseline. Results from this study demonstrated an acceptable safety and tolerability profile of SEP-363856 75 mg/day for up to 28 days in adults with schizophrenia.

Study SEP361-201 was a 4-week, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of SEP-363856 (flexibly-dosed at 50 to 75 mg/day) in acutely psychotic adults with schizophrenia. SEP-363856 demonstrated statistically significant improvement in the PANSS total score compared to placebo at Week 4 (primary endpoint) with an effect size of 0.45. Significant differences favoring the SEP-363856 group were also demonstrated on all secondary efficacy endpoints, including the Clinical Global Impression – Severity scale (CGI-S), PANSS subscales encompassing positive, negative and general psychopathology symptoms, the Montgomery-Asberg Depression Rating Scale (MADRS) and Brief Negative Symptom Scale (BNSS). Overall, the safety and tolerability profile were comparable to placebo. There were no clinically relevant findings related to electrocardiogram (ECG) parameters, laboratory parameters, vital signs, motor symptoms or suicidality.

Study SEP361-202 is a, long-term, open-label extension study to Study SEP361-201, which is evaluating the safety and tolerability of flexibly dosed SEP-363856 (25, 50, or 75 mg/day) in adults with schizophrenia for up to 26 weeks. A total of 156 subjects received SEP-363856 in Study SEP361-202 (79 subjects randomized previously to placebo in Study SEP361-201). In Study SEP361-202, the most common AEs were schizophrenia, headache, insomnia, and anxiety.

Together, these data support continued development of SEP-363856 as a potential treatment for patients with schizophrenia.

The present study is a 52-week, outpatient, multicenter, parallel-group, flexible-dose study, designed to evaluate the long-term safety and tolerability of SEP-363856 (50 to 100 mg/day) compared with quetiapine XR (400 to 800 mg/day) in clinically stable adult subjects with schizophrenia.

4.3. Risk-Benefit Assessment

Schizophrenia is a lifelong disorder and despite advances in drug treatment many patients continue to experience significant symptoms, disabling side effects and impaired functioning and quality of life. Some patients respond poorly to currently available antipsychotics and continue to have symptoms and substantial functional/cognitive impairment (Keefe-2006; Webber-2008).

Antipsychotic treatment is associated with medically-important adverse effects, including weight gain, metabolic syndrome, sedation, extrapyramidal symptoms (including akathisia), hyperprolactinemia and QT interval prolongation (Davis-2004; Lieberman-2005; Newcomer-2007; Leucht-2009). These side effects are attributable to both on-target (D_2) and off-target receptor binding. A significant unmet need still exists for treatments with better efficacy, safety and tolerability.

SEP-363856 has a novel mechanism of action and does not functionally modulate the D_2 receptor nor any of the receptors shown to impart significant side effects of currently approved antipsychotics.

In an adequate and well-controlled four-week double-blind study in adults with schizophrenia (Study SEP361-201), SEP-363856 demonstrated a statistically significant improvement in Positive and Negative Syndrome Scale (PANSS) total score compared to placebo with an effect size of 0.45, supporting antipsychotic efficacy. The effectiveness of treatment with SEP-363856 was also shown to be sustained over a 6-month extension period (Study SEP361-202). Overall, the safety and tolerability profile of SEP-363856, including rates of extrapyramidal symptoms and hyperprolactinemia, was comparable to placebo. Notably, no clinically significant mean changes from baseline in lipid or glucose parameters were found, nor was weight gain observed in association with SEP-363856 treatment.

SEP-363856 has the potential to provide a significantly improved safety profile compared to available therapy, while providing efficacy in the treatment of patients with schizophrenia. Data generated in the clinical program to date provide an acceptable expected benefit/risk ratio for evaluating SEP-363856 in adults with schizophrenia in this study.

4.4. Hypothesis

This study is intended to evaluate the long-term safety and tolerability of SEP-363856.

5. STUDY OBJECTIVES

5.1. Primary Objective

To evaluate the long-term safety and tolerability of flexibly-dosed SEP-363856 (50, 75, and 100 mg/day) in clinically stable adult subjects with chronic schizophrenia based on safety parameters, including the incidence of overall adverse events (AEs), serious AEs (SAEs) and AEs leading to discontinuation.

5.2. Other Safety Objectives

To evaluate the long-term safety and tolerability of SEP-363856 by assessing:

- physical examinations (PE)
- 12-lead electrocardiograms (ECG)
- vital sign measurements
- clinical laboratory tests
- suicidality using the Columbia – Suicide Severity Rating Scale (C-SSRS)
- movement disorder abnormalities using the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS)
- To evaluate the effects of SEP-363856 (50 to 100 mg/day) on prolactin, HbA1c, lipids, and glucose concentration, body weight, and body mass index (BMI) compared to quetiapine XR (400 to 800 mg/day).
- To evaluate the impact of SEP-363856 on healthcare resource utilization.

5.3. Other Efficacy Objectives

- To evaluate the long-term effectiveness of SEP-363856 and quetiapine XR using the
  - Positive and Negative Syndrome Scale (PANSS)
  - Clinical Global Impression-Severity (CGI-S) scale
  - Brief Negative Symptom Scale (BNSS)
  - Montgomery-Asberg Depression Rating Scale (MADRS)
- To evaluate the maintenance efficacy of SEP-363856 and quetiapine XR (including time to relapse, rate of relapse and frequency of hospitalization due to relapse)
- To evaluate adherence to study treatment based on time to all cause discontinuation
- To evaluate the effects of SEP-363856 and quetiapine XR on daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS)
- To assess the effects of SEP-363856 and quetiapine XR on cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS)

- To explore the effects of SEP-363856 and quetiapine XR on functional capacity as measured by the University of California San Diego (UCSD) Performance-Based Skills Assessment – Brief Version (UPSA-B).
- To evaluate the effects of SEP-363856 and quetiapine XR on function as measured by the Specific Level of Functioning Scale (SLOF)
- To evaluate the effects of SEP-363856 and quetiapine XR on health-related quality of life as measured by the EuroQol-5D-5L (EQ-5D-5L)
- To evaluate medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ)
- To explore the impact of SEP-363856 on nicotine use

5.4. CCI

6. STUDY ENDPOINTS

6.1. Primary Endpoints

- The incidence of overall AEs, SAEs, and AEs leading to discontinuation

6.2. Other Safety Endpoints

- Observed values and changes from Baseline in clinical laboratory tests (hematology, chemistry and urinalysis)
- 12-lead ECG (including heart rate, RR, PR, QRS, QT, QTc-F and QTc-B)
- Observed values and changes from Baseline in vital signs (including body weight, BMI, waist circumference, temperature, blood pressure [supine and standing], heart rate [supine and standing] and respiratory rate)
- Frequency and severity of suicidal ideation and suicidal behavior based on the C-SSRS
- Changes from Baseline in BARS, AIMS and SAS scores
- Healthcare resource utilization (HRU) (including numbers of physician office visits, ER visits and hospitalizations, length of hospital stays, employment status and average number of hours caregiver spends helping subjects per week).

6.3. Other Efficacy Endpoints

- Changes from Baseline in:
  - PANSS total score and subscale scores (positive, negative, and general psychopathology)
  - CGI-S score
  - BNSS total score
  - MADRS total score
  - ESS total score
  - BACS composite score
  - UPSA-B total score
  - SLOF total and subscale scores
  - EQ-5D-5L visual analog scale (VAS), index score and dimension score
  - MSQ score
- Time to relapse, rate of relapse, and frequency of hospitalization due to relapse. Relapse will be defined as the earliest occurrence of any of the following:
  - Worsening of > 30% PANSS total score from Baseline and CGI-S > 3
  - Hospitalization for worsening of psychosis

  - Emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others
  - Discontinuation from the study due to exacerbation of the underlying illness of schizophrenia
- Time to all cause discontinuation from the study
- Change from Baseline in tobacco use
- Plasma cotinine concentrations

6.4. CCI

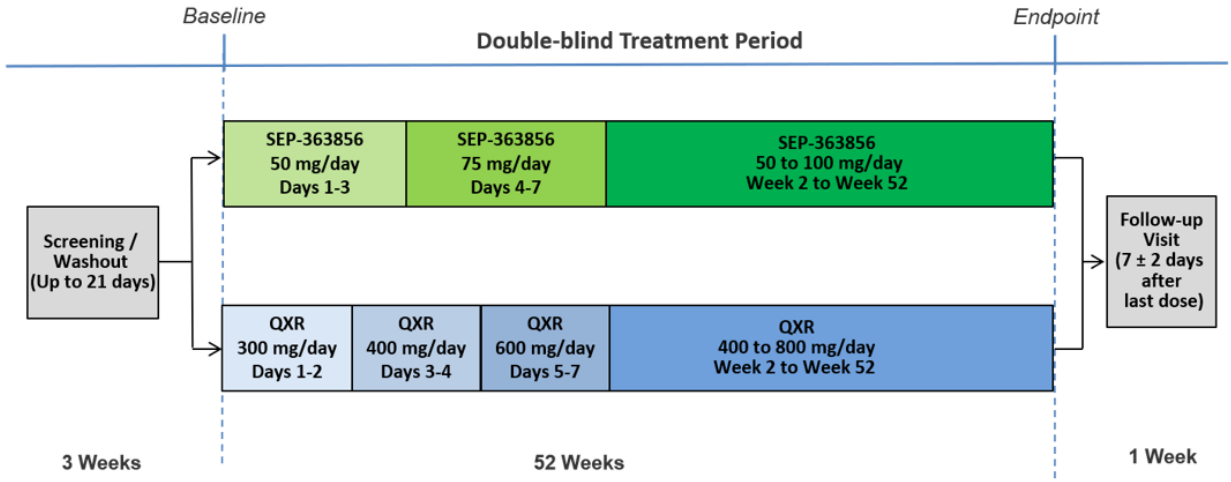
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 52-week, multicenter, randomized, double-blind, parallel-group, flexible-dose study designed to evaluate the long-term safety and tolerability of SEP-363856 (50 to 100 mg/day) in clinically stable adults with schizophrenia. This study is projected to randomize approximately 300 subjects to two treatment groups (SEP-363856 50 to 100 mg/day or quetiapine XR 400 to 800 mg/day) in a 2:1 ratio. Study drug will be taken at the same time each evening at bedtime and should be taken without food or with a light meal.

The study will consist of three periods: Screening/Washout (up to 21 days), Treatment (52 weeks) and a Follow-up visit (7 days after the last study drug dose) as shown in Figure 1.

Figure 1: Study Schematic



Screening/Washout Period (up to 21 days):

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a Screening/Washout Period of up to 21 days, during which they will be tapered off all psychotropic medications (except as noted in the Concomitant Medications section below) in a manner that is consistent with labeling recommendations and conventional medical practices. The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

Subjects may be hospitalized for up to one week prior to randomization during the Screening/Washout Period, if deemed clinically necessary by the Investigator. Additional hospitalization during the Screening/Washout Period beyond one week may be allowed after approval from the Medical Monitor.

Subjects who screen fail may be re-screened once, if judged appropriate by the Investigator after discussion with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

Double-Blind Treatment Period (52 weeks):

At Baseline (Day 1), subjects who have successfully completed the washout of psychotropic medications and have met the eligibility criteria will be randomly assigned via interactive web response system (IWRS) to SEP-363856 or quetiapine XR treatment groups in a 2:1 ratio. Study drug dosing will begin the evening of the Baseline visit. Treatment will continue once-daily, in the evening at bedtime, for the remainder of the Treatment Period, during which the procedures outlined in Table 2 will be conducted. Subjects will be seen at Baseline, Weeks 1, 2 and 4, and then every 4 weeks thereafter up to Week 52. Telephone calls will be made by a member of the clinical research staff to the subjects weekly between visits that are more than one week apart to collect AEs and concomitant medications, as well as to remind subject about adherence to study drug administration and upcoming visits.

Subjects may be hospitalized for the first 7 days of the Treatment Period, if deemed clinically necessary by the Investigator. Further hospitalization during the Treatment Period will require approval from the Medical Monitor.

Subjects randomized to the SEP-363856 group will receive SEP 363856 50 mg/day from Day 1 through Day 3 and 75 mg/day from Day 4 through Day 7. Beginning on Day 8, the dose can be adjusted among 3 dose levels (50, 75 and 100 mg), as deemed clinically appropriate by the Investigator.

Subjects randomized to the quetiapine XR group will receive quetiapine XR 300 mg/day on Days 1 and 2, 400 mg/day on Days 3 and 4, and 600 mg/day from Day 5 through Day 7. Beginning on Day 8, the dose can be adjusted among 3 dose levels (400, 600, and 800 mg), as deemed clinically appropriate by the Investigator.

Dose adjustments made to either SEP-363856 or quetiapine XR will be done in a blinded fashion.

Dose increases can be made no more frequently than weekly to the next higher dose level beginning on Day 8, if the response to the previous dose level is not adequate and there are no significant tolerability problems, based on Investigator judgement. Increases in dose will occur at regularly scheduled study visits, when possible. However, dose increases between regularly scheduled visits may occur (as long as subject have been taking the previous dose level for at least 7 days). If a dose increase is performed between regularly scheduled visits, subjects will be required to return to the clinic at an unscheduled visit for drug dispensation.

Dose reductions can be made to the next lower dose level at any time (at least 1 day apart) beginning on Day 8 for tolerability issues as judged by the Investigator. If a dose reduction is needed between study visits, subjects will be asked to return to the clinic for an unscheduled visit for drug dispensation.

For subjects who have received study drug and who prematurely discontinue from the study treatment, every effort should be made to complete the final evaluation procedures within 48 hours of the last study drug dose at the early termination (ET) visit.

Follow-up Period (1 week):

Subjects who discontinue early from the study or complete study will be required to complete the Follow-up Visit 7 days (± 2 days) post last dose of study drug.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

This is a randomized, double-blind, active comparator-controlled study.

Randomization will be stratified by country. The randomization schedule will be generated by a non-study biostatistician. Once a subject is deemed eligible to be randomized at Day 1, an IWRS will perform treatment assignment. Subjects will be randomized to one of the following treatment groups in a 2:1 ratio:

- Flexibly dosed SEP-363856 (50, 75, or 100 mg/day) for 52 weeks
- Flexibly dosed quetiapine XR (400, 600, or 800 mg/day) for 52 weeks

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

7.2.2. Blinding

Subjects, Investigators, clinical site staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories will remain blinded to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding in the IWRS, and will not be accessible by anyone else involved in the study with the following exceptions: bioanalytical laboratory personnel involved in the analysis of PK samples, Data and Safety Monitoring Board (DSMB) members involved in regular review of safety data, external statistical staff involved in preparing materials for DSMB reviews, pharmacovigilance department for evaluation and reporting of SAEs, and the Sponsor's clinical trial materials management.
- Prolactin levels will be blinded except for results from Visit 1 (Screening).
- 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.
- CCI [redacted]

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 IWRS. 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 11.7.17. The identity of those individuals at the study site who gain access to the unblinded treatment assignment must be documented. It is mandatory that all personnel who are involved in the unblinding, and who have access to the unblinded

treatment assignment, maintain the confidentiality of the information and do not divulge the treatment assignment.

7.3. Rationale

7.3.1. Rationale for the Study Design

Schizophrenia is a chronic disorder requiring long-term treatment and follow-up care. This study will evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (50, 75 or 100 mg/day) and the active comparator quetiapine XR (400, 600, or 800 mg/day) in adults with schizophrenia.

7.3.2. Rationale for the Dosages

In the present study, flexible dosing of SEP-363856 50, 75 or 100 mg/day for 52 weeks will be investigated.

Selection of these doses was guided by the development program to-date, including the maximum tolerated dose (MTD) determined for single doses of SEP-363856 administered to subjects with schizophrenia in Study SEP361-105 (100 mg); by the single doses administered to healthy adult subjects in Studies SEP361-103 and SEP361-104 (50 mg) which were found to have robust CNS activity and by the results from Study SEP361-201, which demonstrated that SEP-363856 flexibly dosed at 50 to 75 mg/day was well-tolerated and showed a statistically significant improvement from Baseline to Week 4 in PANSS total score for SEP-363856 versus placebo in adults with an acute exacerbation of schizophrenia. SEP-363856 (flexibly dosed at 25, 50, or 75 mg/day) was also well tolerated in the 6-month, open-label extension study SEP361-202.

The MTD for multiple doses of SEP-363856 in adults with schizophrenia was previously determined to be 75 mg/day (Study SEP361-106). In Study SEP361-106, as more than 50% of SEP-363856 subjects in 100 mg/day cohort (5 of 9 subjects) experienced multiple moderate AEs assessed as related to SEP-363856 the protocol defined MTD for multiple daily oral administration of SEP-363856 to adults with schizophrenia was determined as 75 mg/day. The moderate AEs assessed as related to SEP-363856 experienced by more than 1 subject in the 100 mg/day dose group were somnolence and dizziness, none of which resulted in treatment discontinuation. However, in Study SEP361-201, where the majority of subjects received 75 mg/day for 4 weeks, the tolerability and safety profile was shown to be similar to that of placebo. This indicates that a dose higher than 75 mg/day may be tested to maximize efficacy, based on an acceptable expected benefit/risk ratio. In Study SEP361-201, subjects were required to receive 50 mg/day for at least 3 days before titrating up to 75 mg/day. In this study (SEP361-304), titration to the 75 and 100 mg/day dosages is included to improve tolerability.

The quetiapine XR dose range is consistent with labeling recommendations.

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:

- Some concomitant psychotropic medications are allowed, as needed, during study participation.
- Dose reductions (or SEP-363856 from 100 to 75 mg/day; or from 75 to 50 mg/day; For quetiapine XR from 800 to 600 mg/day; or from 600 to 400 mg/day) are allowed for drug tolerability purposes.
- Study centers are trained 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.
- Telephone calls will be made by a member of the clinical research staff to the subjects weekly between visits that are more than one week apart to collect AEs and concomitant medications, as well as to remind subject about adherence to study drug administration and upcoming visits.
- Data collection is monitored for adherence during the study.

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. In the Investigator's opinion, the subject is appropriate for this study and is willing and able to comply with the protocol, including taking study medication, attending required visits and adhering to study procedures.
3. Subject must be able to understand and follow verbal and written instructions.
4. Male or female subject between 18 to 65 years of age (inclusive) at the time of consent.
5. Subject meets DSM-5 criteria for a diagnosis of schizophrenia as established by clinical interview at Screening (using the DSM-5 as a reference and confirmed using the SCID-CT). The time since the subject's diagnosis must be ≥ 1 year prior to Screening.
6. Every attempt should be made to obtain medical records or to have correspondence with a previous or current treating psychiatrist for the purposes of confirming that the previous course and treatment is consistent with schizophrenia. Every attempt should also be made to obtain medical records for any preexisting medical conditions that may impact a subject's eligibility.
7. Subject must have a CGI-S score ≤ 4 at Screening and Baseline.
8. Subject must have a PANSS total score ≤ 80 at Screening and Baseline.
9. Subject is judged to be clinically stable (i.e., no evidence of an acute exacerbation) by the Investigator for at least 8 weeks prior to Baseline.
10. Subject has had no change in antipsychotic medication(s) (minor dose adjustments for tolerability purposes are permitted) for at least 6 weeks prior to Screening.
11. Subjects taking an antipsychotic agent at Screening may participate in this study only if there are signs of intolerability or lack of efficacy of the current antipsychotic (as determined by the Investigator).
12. Subject's BMI must be 18 kg/m^2 to 35 kg/m^2 (inclusive) at Screening.
13. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening.
14. Female subjects of childbearing potential must agree to 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. Details on contraception requirements are provided in Section 10.5.
15. Male subjects must agree to avoid fathering a child and to use highly effective methods of birth control from screening until at least 30 days after the last study drug administration. Details on contraception requirements are provided in Section 10.5.

16. Subject is, in the opinion of the Investigator, generally healthy based on Screening medical history, PE, neurological examination, vital signs, electrocardiogram (ECG) and clinical laboratory values (hematology, chemistry and urinalysis).
17. Subject has a stable living arrangement at the time of Screening and intends to remain in a stable living arrangement for the course of the study.
18. Subject's eligibility confirmed through formal adjudication process (See Section 10.7).

8.2. Subject Exclusion Criteria

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

1. Subject was hospitalized for a psychiatric illness within the 8 weeks prior to Screening.
2. Subject has a current DSM-5 diagnosis or presence of symptoms consistent with a DSM-5 diagnosis other than schizophrenia. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months or for a total of ≥ 10 years during the subject's lifetime), substance (other than nicotine or caffeine) use disorder within past 12 months or for a total of ≥ 10 years during the subject's lifetime, major depressive disorder, schizoaffective disorder, bipolar I or II disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms are not the primary focus of treatment.
3. Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents within a 1-year period prior to Screening, given at adequate dose as per labeling, for at least 4 weeks.
4. 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 Screening (i.e., in the past one month) or at Baseline (i.e., since last visit).
5. Subject is at significant risk of harming self or others based on Investigator's judgment.
6. Subject has attempted suicide within 6 months prior to Screening.
7. Subject has received treatment with a psychotropic medication or herbal supplement within 3 days or 5 half-lives (whichever is longer) prior to randomization or anticipates the need for psychotropic medications or herbal supplements during their participation in this study, with the exception of the medications specified in Section 10.3.5. The following medications have additional washout requirements as specified below:
    - Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to randomization.
    - Fluoxetine must be discontinued at least 28 days prior to randomization.
    - Clozapine used at 200 mg/day or less for insomnia, agitation or anxiety must be discontinued at least 28 days prior to randomization. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation.

- Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to randomization.

8. Subject has received electroconvulsive therapy (ECT) treatment within the 3 months prior to Screening or is expected to require ECT during the study.
9. Subject has been treated with quetiapine or quetiapine XR within the 6 weeks prior to Screening or has a history of inadequate response or intolerability to quetiapine or quetiapine XR.
10. 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 (including unstable hypertension), hepatic, neurologic, or allergic disease that is clinically significant or unstable (except for seasonal allergies). **Note: Any subject with a known cardiovascular disease or condition, including hypertension, (even if under control and considered stable) must be discussed with the Medical Monitor before being randomized in the study.**
    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.
    d. Subject has a history of pituitary tumors of any duration.
    e. Disorder or history of a gastrointestinal condition or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, or bowel resection) that may interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or gastric pH.
    f. Subject has a history of malabsorption.
    g. Subject has a clinically significant abnormal 12-lead ECG that may jeopardize the subject's ability to complete the study or that may confound study results as determined by the Investigator, or a Screening centrally overread 12-lead ECG demonstrating any one of the following: heart rate > 100 beats per minute, heart rate < 50 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. Subjects with an ECG that has a centrally overread overall interpretation of "abnormal, significant" or "abnormal, potentially clinically significant" must be discussed with the Medical Monitor.
    h. Subjects with known history of human immunodeficiency virus (HIV) seropositivity.
    i. Subject has type I diabetes mellitus or insulin-dependent type II diabetes.
11. Subject exhibits evidence of moderate or severe extrapyramidal symptoms, dystonia, tardive dyskinesia, or any other moderate or severe movement disorder. Severity to be determined by the Investigator.

12. Female subject who is pregnant or lactating.
13. Subject has a history of allergic reaction or suspected sensitivity to quetiapine or quetiapine XR or any substance that is contained in the quetiapine XR or SEP-363856 formulations.
14. Subject with a supine systolic blood pressure ≥ 140 mmHg and/or supine diastolic blood pressure ≥ 90 at Screening or Baseline. A repeat blood pressure measurement is allowed once during the Screening Period and once at Baseline. The repeat measurements can be used to determine eligibility. The repeat blood pressure measurement at Screening can be conducted on a different day within the screening period, if needed.
15. Subject has any clinically significant abnormal laboratory value(s) at Screening (hematology, chemistry and urinalysis) as determined by the Investigator. (Note: Retesting is allowed once during the Screening Period and the retest will be used to determine eligibility after approval from the Medical Monitor; however, the Screening Period will not be extended to accommodate repeat laboratory tests, unless repeat tests are needed due to a technical issue with laboratory sample processing, shipment or testing delay at the central laboratory. Abnormal findings of questionable significance will be discussed with the Medical Monitor prior to including any subject.)
16. Subject demonstrates evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation. Subjects who test positive for hepatitis C antibody at Screening and have a positive or indeterminate confirmatory test for hepatitis C are excluded. Subjects who test positive for hepatitis B surface antigen at screening are excluded.
17. Subjects with ALT or AST ≥ 3 times the upper limit of the reference ranges provided by the central laboratory at Screening.
18. Subject has a serum blood urea nitrogen (BUN) or serum creatinine (Cr) value ≥ 1.5 times the upper limit of normal of the reference range provided by the central laboratory at Screening.
19. Subjects with a fasting blood glucose at Screening ≥ 126 mg/dL (7.0 mmol/L) or HbA_{1c} > 7.0%.
20. Subject has a prolactin concentration > 200 ng/mL at Screening. Subjects with prolactin levels > 100 ng/mL and ≤ 200 ng/mL at Screening are eligible only after discussion with the Medical Monitor to ensure exclusion of non-psychotropic drug-related causes of elevated prolactin levels.
21. Subject tests positive for drugs of abuse at Screening. However, a positive urine drug screen may not result in exclusion of subjects if the investigator determines that the positive test is a result of prescription medicine(s). Subjects who test positive for cannabinoids (tetrahydrocannabinol or cannabidiol) at Screening are excluded.
22. Subject has received an investigational product or device within 1 year prior to signing informed consent or has participated in more than 2 studies in psychiatric indications of investigational products or devices within their lifetime.
23. Subject has previously received SEP-363856.

24. Subject is a staff member of the study center or the relative of a staff member of the study center.
25. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

SEP-363856 active and placebo tablets will be over-encapsulated in size DB AAel hard gelatin capsules and back filled with microcrystalline cellulose. SEP-363856 active tablets including 50 mg, 75 mg and 100 mg and the matching placebo will be utilized. To maintain the blind, over-encapsulated placebo will also be used as part of the blister cards (refer to Section 9.2.1).

Quetiapine XR tablets (300 mg and 400 mg) will be over-encapsulated in Size DB AAel Swedish orange capsules and back filled with microcrystalline cellulose.

Table 5: Over-Encapsulated Drug Product

Attribute						
Product name	**SEP-363856**	**SEP-363856**	**SEP-363856**	**Placebo**	**Seroquel XR**	**Seroquel XR**
Dosage form	**Tablet**	**Tablet**	**Tablet**	**Tablet**	**Tablet**	**Tablet**
Unit dose	**50 mg**	**75 mg**	**100 mg**	**N/A**	**300 mg**	**400 mg**
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Physical description	Swedish orange capsule containing one yellow oval tablet and white powder	Swedish orange capsule containing one yellow oval tablet and white powder	Swedish orange capsule containing one yellow oval tablet and white powder	Swedish orange capsule containing one yellow oval tablet and white powder	Swedish orange capsule containing one pale yellow capsule-shaped tablet engraved with "XR 300" and white powder	Swedish orange capsule containing one white capsule-shaped tablet engraved with "XR 400" and white powder
Active Pharmaceutical ingredient (API)	SEP-363856-01 (hydrochloride salt)	SEP-363856-01 (hydrochloride salt)	SEP-363856-01 (hydrochloride salt)	N/A	Quetiapine fumarate	Quetiapine fumarate
Excipients	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Lactose monohydrate - Microcrystalline cellulose -Sodium citrate - Hydroxypropyl methylcellulose -Magnesium stearate Film coating: - Hydroxypropyl methylcellulose -Polyethylene glycol 400 -Titanium dioxide -Yellow iron oxide	-Lactose monohydrate - Microcrystalline cellulose -Sodium citrate - Hydroxypropyl methylcellulose -Magnesium stearate Film coating: - Hydroxypropyl methylcellulose -Polyethylene glycol 400 -Titanium dioxide

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in one-week blister cards containing 18 capsules arranged in 9 columns and 2 rows. Each card will have a unique number identifier. Cards will contain capsules for 9 days (7 days + 2 extra days). Some cards will utilize placebo capsules to maintain the blind. Subjects will be instructed to take a column of 2 capsules each day, according to dosing instructions. Some doses require 2 active capsules, while others only require 1.

Week 1: Blinded Titration Dose

Day	1	2	3	4	5	6	7	Extra day	Extra day
Row 1	SEP-363856 50 mg or QXR 300 mg	SEP-363856 50 mg or QXR 300 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 75 mg or QXR 400 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg
Row 2	Placebo	Placebo	Placebo	Placebo	Placebo or QXR 300 mg	Placebo or QXR 300 mg	Placebo or QXR 300 mg	Placebo or QXR 300 mg	Placebo or QXR 300 mg

Weeks 2 to 52: Blinded Low Dose

Day	1	2	3	4	5	6	7	Extra day	Extra day
Row 1	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg	SEP-363856 50 mg or QXR 400 mg
Row 2	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Weeks 2 to 52: Blinded Middle Dose

Day	1	2	3	4	5	6	7	Extra day	Extra day
Row 1	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg	SEP-363856 75 mg or QXR 300 mg
Row 2	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg	Placebo Or QXR 300 mg

Weeks 2 to 52: Blinded High Dose

Day	1	2	3	4	5	6	7	Extra day	Extra day
Row 1	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg	SEP-363856 100 mg or QXR 400 mg
Row 2	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg	Placebo or QXR 400 mg

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 tablets)
- 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 drug should be stored between 20°C and 25°C (68° to 77°F). Excursions of 15°C to 30°C (59°F to 86°F) are permitted during shipment of study drug to investigational sites (see United States Pharmacopeia [USP]).

9.4. Dispensing of Study Drug

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

Study drug blister cards will be assigned by the IWRS based on the treatment schedule and dose adjustment criteria. The IWRS will generate instructions for which blister card ID(s) to dispense to the subject. Each subject will be dispensed one to four 9-day (7 days + 2 days extra days) blister cards per scheduled visit depending on the timing of the next scheduled visit (see Table 2). IWRS drug dispensing guidelines should be followed for dispensing study drug to subjects. A specific user manual will be provided.

Subjects will take two blinded capsules (one from each row) of study drug per day at approximately the same time each evening at bedtime. Study drug may be taken without food or with a light meal.

9.5. Study Drug Accountability

The investigator or designee is responsible for maintaining adequate and up to date records of drug disposition that includes dates, quantities, and use by subjects.

Upon receipt of study drug, the Investigator or designee will inspect the supplies and verify receipt of the shipment in the IWRS, confirming the date of receipt, inventory and condition of study drug received.

The IWRS will also be used for the accountability of the study drug at the clinical site. The Investigator or designee will maintain records for accountability within the IWRS, including study drug dispensation, return and availability of study drug received. The Investigator or designee will collect and document the status of all used and unused study drug from study subjects at appropriate study visits.

9.6. Study Drug Handling and Disposal

The Investigator or designee is responsible for storing the study drug in a secure location. Study drug should be maintained under the strict control of qualified site staff at all times. Proper handling and storage guidelines should be followed.

If the study is stopped for any reason or completed, all unused supplies will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/contract research organization (CRO).

The Investigator or designee is required to return all used and unused 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.

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

10. TREATMENT OF SUBJECTS

10.1. Study Medication

All doses of study drug consist of SEP-363856 50 mg, 75 mg or 100 mg tablets and quetiapine XR tablets 300 mg and 400 mg, administered in capsule form orally once daily and will be supplied as described in Section 9.

Subjects may take study drug without food or with a light meal at approximately the same time each evening at bedtime.

10.1.1. Dose Adjustment Criteria

Subjects randomized to the SEP-363856 group will receive SEP-363856 50 mg/day from Day 1 through Day 3 and 75 mg/day from Day 4 through Day 7. Beginning on Day 8, the dose can be adjusted among 3 dose levels (50, 75 and 100 mg), as deemed clinically appropriate by the Investigator.

Subjects randomized to the quetiapine XR group will receive quetiapine XR 300 mg/day on Days 1 and 2, 400 mg/day on Days 3 and 4, and 600 mg/day from Day 5 through Day 7. Beginning on Day 8, the dose can be adjusted among 3 dose levels (400, 600, and 800 mg), as deemed clinically appropriate by the Investigator.

Dose adjustments made to either SEP-363856 or quetiapine XR will be done in a blinded fashion.

Dose increases can be made no more frequently than weekly to the next higher dose level beginning on Day 8, if the response to the previous dose level is not adequate and there are no significant tolerability problems, based on Investigator judgement. Increases in dose will occur at regularly scheduled study visits, when possible. However, dose increases between regularly scheduled visits may occur (as long as the subject has been taking the previous dose level for at least 7 days). If a dose increase is performed between regularly scheduled visits, subjects will be required to return to the clinic at an unscheduled visit for drug dispensation.

Dose reductions can be made to the next lower dose level at any time (at least 1 day apart) beginning on Day 8 for tolerability issues as judged by the Investigator. If a dose reduction is needed between study visits, subjects will be asked to return to the clinic for an unscheduled visit for drug dispensation.

10.2. Treatment Compliance

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

Compliance must be monitored closely and determined at each visit. Subjects will be instructed to bring all used blister cards and unused study drug with them to 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

Prior use of psychotropic medication during the previous 3 years, and any other medication taken during the previous 60 days will be recorded at Visit 1 (Screening).

Details on all medications taken in the 60 days prior to Screening (including dosing changes) will be recorded. For psychotropic medications taken prior to that 60-day period, approximate start and stop dates of each unique psychotropic medication will be recorded, along with the maximum daily dose of the psychotropic medication ever taken during the specified time period (i.e., it is not required to capture every psychotropic dose change during this period).

Every effort should be made to collect medical and/or pharmacy records for psychotropic medications used in the past 3 years and non-psychotropic medications used in the past 60 days on the eCRF. However, if medical records cannot be obtained, prior medications are to be reported based on subject and caregiver/informant report.

Thereafter, any changes in concomitant medications or new medications added up to the Follow-up Visit from the study will be recorded. At a minimum, the following information on prior and concomitant medications will be recorded on the case report form (CRF): Medication name, dose, frequency, route, start date and time, stop date and time, 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).

10.3.1. Prior Medications:

Treatment with oral psychotropic medications and any other medications with a propensity for psychotropic effects (with the exception of the medications described below under Allowed Concomitant Psychotropic Medications) must be discontinued at least 3 days or 5 half-lives (whichever is longer) prior to randomization in a manner that is consistent with labeling recommendations and conventional medical practice.

The following psychotropic medications have additional washout requirements:

- MAO inhibitors must be discontinued at least 28 days prior to randomization.
- Fluoxetine must be discontinued at least 28 days prior to randomization.
- Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to randomization. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for an indication other than insomnia, agitation, or anxiety are excluded from study participation.
- Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to the randomization visit.

Treatment with the sedative hypnotics described in Section 10.3.5 is permitted during the Screening/Washout Period but should be tapered as clinically appropriate to conform with and

adequately prepare the subject for the protocol-specified limitations applicable to these agents following randomization. Subjects should not be taken off their current effective medications for treatment of schizophrenia for purposes of participating in this study.

Treatment with medications used to treat movement disorders must be discontinued at least 1 day prior to randomization.

10.3.2. Prohibited Medications

Psychotropic medications and medications with a propensity for psychotropic effects are not permitted during the Treatment Period, except for the medications discussed in Section 10.3.5. Use of psychotropic medications is permitted after the last dose of study medication provided they are not administered prior to the final PANSS assessment.

The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications are not permitted during the Treatment Period; however, they are permitted after the last dose of study medication provided they are not administered prior to the final PANSS assessment.

Subjects who are administered a psychotropic medication (other than the study drug and the acceptable medications discussed in Section 10.3.5) for the purposes of treating an exacerbation of symptoms associated schizophrenia or due to lack of efficacy of the study treatment will be discontinued from the study.

10.3.3. Prohibited Therapies

Subjects must not receive electroconvulsive therapy (ECT) during the study up through the Follow-up Visit. Subjects who received ECT treatment during the Treatment Period will be discontinued from the study.

10.3.4. Concomitant Nonpsychotropic Medications

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% total daily dose) for at least 30 days prior to screening. The dose for the concomitant medication may change, as needed, after randomization (or be discontinued). This includes β-adrenergic antagonists used to treat stable hypertension. Routine vaccines (i.e., seasonal influenza, pneumonia, etc.) are allowed based on the investigator's judgment. Female subjects may use contraception as detailed in Section 10.5.

In addition, use of non-prescription pain medications (e.g., aspirin, acetaminophen/paracetamol, ibuprofen) are allowed during the study provided these medications do not have a propensity for psychotropic effects.

The Medical Monitor should be consulted, if possible, before administering medications for short-term treatment of an acute medical condition. If medications are administered for short-term treatment of an acute medical condition without prior consultation with the Medical Monitor, the Medical Monitor is to be informed of such medication use as soon as possible and the appropriateness for the subject to continue in the study should be discussed with the Medical Monitor.

10.3.5. Allowed Concomitant Psychotropic Medications

Treatment with benztropine (benzotropine outside the United States [US]) up to 6 mg/day is permitted, as needed, for motor symptoms. 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) is permitted as needed for akathisia. These allowed medications for the treatment of EPS and akathisia may be given in any formulation (oral, intramuscular [IM] or intravenous [IV]) as deemed appropriate by the Investigator. Medications used to treat motor symptoms should not be given prophylactically. They are to be tapered and discontinued 1 day prior to randomization but may be reinstated if symptoms emerge post-randomization during the study.

Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem, zolpidem controlled release (CR), diphenhydramine, and melatonin is permitted at the discretion of the Investigator with the following restrictions:

- Oral 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.
- Diphenhydramine ≤ 100 mg/day and melatonin ≤ 5 mg/day may be administered at bedtime for insomnia, as needed. Over-the-counter melatonin should be used. Combination melatonin products are not allowed.
- Temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, as needed.
- Medications that are used for insomnia should be administered no more than once nightly and should not be used in combination.
- Medications used for the treatment of anxiety/agitation and insomnia (e.g., 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 above specified drugs available, similar drugs at equivalent dosages will be permitted in consultation with the Medical Monitor.

The date and 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 any psychotropic medication (or any agents that may cause sedation) within 8 hours of efficacy assessments.

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

10.4. Other Restrictions

Subjects must abstain from alcohol from enrollment through the end of the study.

10.5. Contraception Requirements

Female subjects who participate in this study must be of:

- Non-childbearing potential (ie, physiologically incapable of becoming pregnant), which includes:
  - Women who have had a hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation or bilateral tubal occlusion (as determined by subject's medical history)

    OR
  - Postmenopausal females, defined as at least 12 months of spontaneous amenorrhea and confirmed by follicle stimulating hormone (FSH) concentrations within postmenopausal range as determined by the central laboratory

-OR-

- Childbearing potential with a negative serum pregnancy test at screening and satisfying one of the following requirements:
  - Completely abstinent from intercourse as part of the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and the withdrawal method are not acceptable methods of contraception. Subject must have been abstinent for at least 60 days prior to administration of the first dose of study drug, throughout the Treatment Period and for a minimum of 30 days after completion or premature discontinuation from the study drug.
  - Use of highly effective methods of contraception during the Treatment Period and for 30 days after last dose of study drug. Highly effective forms of contraception include:
    - Subcutaneous hormonal implant (such as Norplant®) implanted at least 90 days prior to Screening;
    - Injectable hormonal contraception (such as medroxyprogesterone acetate injection) given at least 14 days prior to Screening;
    - Oral or transdermal hormonal contraception used as directed for at least 30 days prior to Screening.
    - Vaginal ring (eg, NuvaRing®) used as directed for at least 30 days prior to Screening.
    - Intrauterine device implanted at least 30 days prior to Screening.
    - Intrauterine hormone-releasing system implanted at least 30 days prior to Screening.

- Two barrier methods used in combination (eg, condom and spermicide or diaphragm with spermicide). Note: a female condom and a male condom should not be used together due to friction between the 2 barrier methods reducing effectiveness of contraception.

Post-coital methods of contraception are not permitted.

Male subjects with a female partner(s) of childbearing potential must agree to avoid fathering a child and must be surgically sterile (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) or use highly effective methods of contraception from Screening until at least 30 days after the last dose of study drug. Male subjects must also refrain from donation of semen/sperm 30 days prior to administration of the first dose of study drug, during the Treatment Period and for 30 days after last dose of the study drug.

10.6. Guidance for Overdose

Potential overdose to SEP-363856 has not been evaluated. The effects of an overdose of SEP-363856 are unknown and there is no known treatment in case of overdose.

According to SEROQUEL XR® package insert, in clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia, and hypotension.

There is no specific antidote to quetiapine XR.

Appropriate supportive measures should be instituted, and close medical supervision and monitoring should be used in the case of pharmacological effects or overdose until the subject recovers. Consider the possibility of multiple-drug overdose.

10.7. Eligibility Adjudication Process

All subjects will be evaluated by the Sponsor and/or designee to determine their eligibility for the study prior to randomization.

Sites will complete a form for each subject in screening, which provides information that supports the subject's appropriateness for participation in the study. Each form must be approved by the Sponsor or designee prior to the subject being randomized.

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 10.3.5 for a complete description of medications permitted during the study. Prior and concomitant medications will be recorded at Visit 1 (Screening). Thereafter, any changes in concomitant medications or new medications added up to Visit 18 or discontinuation from the study will be recorded.

At a minimum, the following information on prior and concomitant medications will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

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 clinical experience with schizophrenia patients. The administration time is approximately 30 – 40 minutes.

11.4. Efficacy Assessments

Raters will receive specific training regarding each assessment prior to rating for the study. The same rater should be used for a given subject and a given scale whenever possible.

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 (Guy-1976, Kay-1994; Opler-1992; Perkins-2000). The PANSS requires input from an informant (e.g., caregiver, relative, friend, case worker, hospital staff). The PANSS-Informant Checklist (PANSS-IC) will be utilized to capture the information from the informant that is required to rate the PANSS. PANSS raters will be required to meet specific training and education criteria before they are certified to rate for this study.

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 (Kirkpatrick-2011). The measure is comprised of 13 individual items and 6 subscale scores (blunted affect, alogia, avolition, anhedonia, asociality, and distress). The 6 subscale 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 subscale. BNSS raters will be required to meet specific training and education criteria before they are certified to rate for this study.

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. Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS scale (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life or their 'daytime sleepiness'. The questionnaire takes no more than 2 or 3 minutes to answer (Epworth Sleepiness Scale-2019).

11.4.6. Brief Assessment of Cognition in Schizophrenia (BACS)

The BACS assesses six domains of cognition; verbal memory/learning, working memory, motor function, verbal fluency, speed of processing, and executive function. Administration time is approximately 30 minutes.

An electronic tablet-based version of the traditional BACS, called the BAC App, will be used in this study. The BAC App was developed to allow standardized presentation of task instructions and stimuli, audio-recording of responses, and automatized scoring and data management. The BAC App provides a composite measure of cognition, as well as individual scores for each of the cognitive domains noted below. It has been clinically validated in schizophrenia and has demonstrated equivalence with the original pen-and-paper measure (Atkins-2017).

- Verbal Memory/Learning is assessed with the Verbal Memory task. Subjects are presented with a list of 15 words and asked to recall as many words as possible. This procedure is repeated 5 times. The outcome measure is the number of words recalled.
- Working Memory is assessed with the Digit Sequencing task. Subjects are presented with auditory clusters of numbers (e.g., 936) of increasing length and asked to tell the rater the numbers in order from lowest to highest. The outcome measure is the number of correct responses.
- Motor Function is assessed with the Token Motor task. Subjects are presented with tokens and asked to drag them to a center container on the monitor as quickly as possible for 60 seconds. The outcome measure is the number of tokens correctly dragged into the container.
- Verbal Fluency is assessed with Semantic Fluency and Letter Fluency tasks. Subjects are given 60 seconds to generate as many words as possible in a given category (semantic) or for a given letter of the alphabet (letter). The outcome measure for each fluency test is the number of words generated.
- Speed of Processing is assessed with the Symbol Coding task. Subjects are provided a key and asked to fill the corresponding number beneath a series of symbols as quickly as possible for 90 seconds. The outcome measure is the number of correct items.
- Executive Function is assessed with the Tower of London task. Subjects are asked to give the minimum number of times the balls in one picture would need to be moved in order to make the arrangement of balls identical to that in the opposing picture. The outcome measure is the number of correct responses.

The BAC composite score for each participant at a given timepoint is computed by taking the sum of the six scaled test scores and dividing by the standard deviation of the sum of the scaled scores from the index population.

11.4.7. University of California, San Diego, Performance-Based Skills Assessment-Brief (UPSA-B)

The UPSA-B assesses everyday functioning in persons with serious mental illness (Mausbach-2007). The UPSA-B consists of 2 subscales (communication and financial). The UPSA-Brief is a measure of functional capacity in which patients are asked to role-play tasks in 2 areas of functioning: (1) communication and (2) finances. The UPSA-Brief requires approximately 10 – 15 minutes to complete and will be administered by a trained professional.

The raw score of the financial subscale ranges from 0 to 11 and the raw score of communication subscale ranges from 0 to 9. Each subscale score is calculated by dividing the raw score by the highest possible raw score of that subscale and then multiplying by 50, so both subscale scores range from 0 to 50. The UPSA-B total score, calculated as the sum of two subscale scores, ranges from 0 to 100. Higher scores reflect better performance.

11.4.8. Modified Specific Level of Functioning Scale (SLOF)

The SLOF is designed to measure directly observable behavioral functioning and daily living skills of patients with chronic mental illness (Schneider-1983). The modified version of the SLOF used in this study consists of 24 items divided into 2 subscales (Social functioning [comprised of interpersonal relationships] and Community Living Skills [comprised of activities and work skills]). Each item is rated on a 5-point scale. Individual items are summed to determine scores for the total score and the 2 subscales.

The scale will be completed by the Investigator or a member of the research site staff who is familiar with the subject. This assessment should include input from the subject's informant (e.g., family member, friend or caregiver). However, if an informant is not available, the rating will still be administered. For each SLOF rating, the rater will record whether an informant was utilized or not.

11.4.9. Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, patient-rated, rater administered questionnaire that requires the subject to use a 7-point, Likert-type scale to rate how satisfied they are with their current antipsychotic medication (Vernon-2010). The subject will be asked the following question:

- "Overall, how satisfied are you with your current antipsychotic medication"

Subjects will select 1 of 7 potential responses based on their level of satisfaction from (1) extremely dissatisfied to (7) extremely satisfied as follows:

(1) Extremely dissatisfied

(2) Very dissatisfied

(3) Somewhat dissatisfied

(4) Neither dissatisfied nor satisfied

(5) Somewhat satisfied

(6) Very satisfied

(7) Extremely satisfied

11.4.10. EuroQol 5D-5L (EQ-5D-5L)

The EQ-5D is a self-administered, standardized measure of health states consisting of two parts: a) EQ-5D descriptive system consisting of one question in each of five dimensions (mobility, self-care, pain, usual activities, and anxiety), and b) a 20-cm visual analogue health status rating. In the descriptive system, respondents are asked to choose the level that reflects their "own health state today" for each of the five dimensions. Once the data have been collected and a database created, a scoring function is used to assign a value (ie, EQ-5D index score) to self-reported health states from a set of population-based preference weights. Additionally, the 20-cm visual analog scale (EQ-VAS) has endpoints labeled "best imaginable health state" and "worst imaginable health state" that are anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day.

11.4.11. Tobacco Use Information and Plasma Cotinine Concentrations

Information on the use of tobacco at Baseline and during the Treatment Period will be recorded on the eCRF, including type of tobacco used and amount used.

Blood samples taken at Baseline and Weeks 12, 24 and 52 for study drug concentration measurement will also be used for the measurement of cotinine levels. No separate blood samples will be collected for cotinine.

11.5. Safety Assessments

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

AEs and SAEs will be monitored throughout the study at all visits.

11.5.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 21, Appendix II.

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 laboratory must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.5.3. Vital Signs

Blood pressure and pulse rate measurements will be taken in a supine and standing position. 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.

Respiratory rate and temperature will also be measured, and all measurements will be recorded in the eCRF.

Height will be measured without shoes only at Visit 1 (Screening). 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). BMI for all other visits will be derived within the Electronic Data Capture (EDC) system and calculated during statistical analysis. Waist circumference will be measured.

Vital signs should be obtained prior to clinical laboratory collection and performance of an ECG.

Clinically significant changes from screening in vital sign parameters, as determined by the Investigator, will be noted as AEs in the CRF.

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. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. Additional information is provided in Section 20, Appendix I. ECG parameters to be collected include ventricular heart rate (beats/min), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec) and centrally-read overall ECG interpretation (Normal; Abnormal, insignificant; Abnormal, potentially significant; Abnormal, significant) including type of abnormality, if present. QTcF and QTcB will also be reported.

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. All ECG tracings and over-read reports will be reviewed, signed and dated by the Investigator. The Investigator must determine and note the clinical significance of all abnormal ECGs. The same physician should review all ECG reports for a given subject whenever possible.

Any clinically significant changes after Screening, as determined by the Investigator, will be noted as AEs in the CRF. ECGs with possibly drug-related or clinically significant abnormal findings of uncertain causality will be repeated.

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

Complete physical examinations (PE) as well as a neurological examination 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). The neurological exam includes an assessment of general appearance, mental status, cranial nerves, motor system, sensory system, reflexes, coordination, and gait.

Any clinically significant changes after Screening, as determined by the Investigator, will be noted as AEs in the CRF.

11.5.6. Safety Scales

11.5.7. 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, and address rigidity, gait (bradykinesia), tremor, glabellar tap, and salivation (Siddiqui-2009; Simpson-1970). The SAS will be administered by a qualified rater at the site.

11.5.8. 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.

11.5.9. 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.

11.5.10. 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 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 other visits from Visit 2 onward the "Since Last Visit" version of the C-SSRS will be used.

11.5.11. Healthcare Resource Utilization (HCRU)

HCRU will be assessed by recording the following:

- number of physician office visits, emergency room visits, and hospitalizations (total number and number related to schizophrenia) in the previous 3 months
- length of each hospital stay in the past 3 months
- employment status in the past 3 months
- the average number of hours a caregiver(s) spends helping the subject per week (past 3 months)

11.6. CCI

[redacted]

CCI

[redacted]

11.7. Study Visits and Assessments

See Table 2 Schedule of Assessments, for a summary of procedures at each study visit.

Unscheduled visits can be conducted during the study at the discretion of the Investigator.

It is suggested that the rating scales be completed in the following order, if possible:

1. PANSS[a]
2. BNSS
3. MADRS
4. C-SSRS
5. SAS/BARS/AIMS
6. SLOF
7. EQ-5D-5L
8. ESS
9. MSQ
10. BACS
11. UPSA-B
12. HCRU
13. CGI-S

a When administering the PANSS, it is suggested that the informant interview and PANSS-IC be completed prior to the subject interview.

Note: With the exception of the SCID-CT, UPSA-B, C-SSRS and the HCRU all rating assessments will be completed by the rater using an electronic tablet. In the event that the electronic tablet is not available, the rating assessments will be performed by the rater or subject using a paper version of the assessment, with the exception of the EQ-5D-5L which is licensed only for electronic use.

11.7.1. Screening: Visit 1 (Day -21 to -1)

After a subject provides consent, a unique subject number will be assigned at screening by the IWRS, consisting of a 3-digit protocol number, 3-digit site number, and a unique 3-digit subject identifier (eg, the second screened subject from site #005 will be 304005002). Subjects will be numbered consecutively. No subject numbers are to be reused once assigned. This number will track a subject throughout their participation in the study.

Subjects will be evaluated at the Screening Visit to determine their eligibility for the study. 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. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled.

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

Subjects who screen fail may be re-screened once, if judged appropriate by the Investigator, after discussion with the Medical Monitor. Re-screened subjects will be re-consented, assigned a new subject number, and all Visit 1 procedures will be repeated.

The Screening Period may be extended for up to 7 days after approval from the Medical Monitor.

The following procedures will be conducted during this visit:

- Obtain signed informed consent and privacy authorization (if applicable or required by local law) from the subject before conducting any other visit procedures, including informed consent for duplicate subject check (where allowed by local/regional regulations)
- CCI [redacted]
- Review inclusion and exclusion criteria
- Collect prior and concomitant medications
- Obtain demographic information
- Collect adverse events (Note: events occurring prior to first dose of study drug will be identified programmatically as pretreatment events.)
- Collect medical history
- Collect psychiatric history
- SCID-CT
- Physical and neurological examination
- Height and weight; clinical site staff to calculate and record BMI
- Vital sign measurements
- Standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)
- Blood samples for serum pregnancy test (serum human chorionic gonadotropin [β-hCG]) for female subjects of childbearing potential and serum follicle stimulating hormone (FSH) for post-menopausal women or if menopause is suspected.
- Blood sample for hepatitis screening
- Urine sample for urinalysis and urine drug screen (UDS)
- PANSS
- C-SSRS
- CGI-S
- MSQ, only for subjects currently treated with an antipsychotic medication or had been treated with antipsychotic medication within 30 days of screening
- Duplicate subject check (where allowed by local/regional regulations)

11.7.2. Baseline: Visit 2 (Day 1)

The following procedures will be conducted during this visit:

- CCI [redacted]
- Collect prior/concomitant medications
- Tobacco use information
- Vital sign measurements
- Weight (BMI derived in the EDC system)
- Waist circumference
- Standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)
- If subject signed separate genetic informed consent, collect a blood sample for potential pharmacogenomics
- CCI [redacted]
- Urine sample for urinalysis, UDS, and β-hCG (for female subjects).
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS
- ESS
- SLOF
- EQ-5D-5L
- BACS
- UPSA-B
- Healthcare resource utilization
- Collect adverse events (Note: events occurring prior to first dose [on Day 1] of study drug will be identified programmatically as pretreatment events.)
- Review inclusion and exclusion criteria

- Randomize to treatment
- Dispense study drug

11.7.3. Visit 3 (Week 1; Day 8 + 2)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Adverse events monitoring
- Vital signs
- Standard 12-lead ECG
- Fasted Blood sample for clinical laboratory tests (hematology and serum chemistry)
- CCI
- Urine sample for urinalysis and urine drug screen (UDS)
- Urine pregnancy test (β-HcG), female subjects only
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS

11.7.4. Visit 4 (Week 2; Day 15 ± 2)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS

11.7.5. Visit 5 (Week 4; Day 29 ± 2)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Physical/neurological examination
- Vital signs
- Weight (BMI derived in the EDC system)
- Waist circumference
- Standard 12-lead ECG
- Fasted Blood sample for clinical laboratory tests (hematology and serum chemistry)
- CCI
- Urine sample for urinalysis and urine drug screen (UDS)
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS

11.7.6. Visit 6 (Week 8; Day 57 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Adverse events monitoring
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only

- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S

11.7.7. Visit 7 (Week 12; Day 85 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Tobacco use information
- Physical and neurological examinations
- Vital signs
- Weight (BMI derived in the EDC system)
- Waist circumference
- Standard 12-lead ECG
- Fasted Blood sample for clinical laboratory tests (hematology and serum chemistry)
- CCI
- Urine sample for urinalysis and urine drug screen (UDS)
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS
- SLOF
- BACS
- UPSA-B
- HCRU

11.7.8. Visit 8 (Week 16; Day 113 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug

- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S

11.7.9. Visit 9 (Week 20; Day 141 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS

11.7.10. Visit 10 (Week 24; Day 169 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Tobacco use information
- Physical/neurological examinations
- Vital signs
- Weight (BMI derived in the EDC system)
- Waist circumference
- Standard 12-lead ECG
- Fasted Blood sample for clinical laboratory tests (hematology and serum chemistry)
- CCI [redacted]
- Urine sample for urinalysis and UDS

- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS
- ESS
- SLOF
- BACS
- UPSA-B
- HCRU

11.7.11. Visit 11 (Week 28; Day 197 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS

11.7.12. Visit 12 (Week 32; Day 225 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only

- Adverse events monitoring
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S

11.7.13. Visit 13 (Week 36; Day 253 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Physical and neurological examinations
- Vital signs
- Weight (BMI derived in the EDC system)
- Waist circumference
- Standard 12-lead ECG
- Fasted Blood sample for clinical laboratory tests (hematology and serum chemistry)
- CCI
- Urine sample for urinalysis and urine drug screen (UDS)
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS
- HCRU

11.7.14. Visit 14 (Week 40; Day 281 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring

- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S

11.7.15. Visit 15 (Week 44; Day 309 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS

11.7.16. Visit 16 (Week 48; Day 337 ± 3)

The following procedures will be conducted during this visit:

- Concomitant medication review
- Study drug accountability
- Dispense study drug
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S

11.7.17. Visit 17 (Week 52; Day 365 ± 3) / End of Treatment (EOT) / Early Termination (ET)

The following procedures will be conducted during this visit:

- Concomitant medication review

- Study drug accountability
- Tobacco use information
- Physical/neurological examinations
- Vital signs
- Weight (BMI derived in the EDC system)
- Waist circumference
- Standard 12-lead ECG
- Fasted Blood sample for clinical laboratory tests (hematology and serum chemistry)
- CCI
- Urine sample for urinalysis and UDS
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- SAS
- BARS
- AIMS
- ESS
- SLOF
- EQ-5D-5L
- BACS
- UPSA-B
- MSQ
- HCRU

11.7.18. Visit 18 (Follow-up 7 ± 2 days after last dose)

All subjects who discontinue early or complete the study will have a safety follow-up visit 7 ± 2 days after their last dose of study drug. While every effort should be made to complete the Follow-up Visit in the clinic, AEs and concomitant medications may be collected by telephone contact if subject is unable to come to the clinic for the Follow-up Visit.

The following procedures will be conducted during this visit:

- Concomitant medication review
- Physical/neurological examination
- Vital signs
- Urine pregnancy test (β-HcG), female subjects only
- Adverse events monitoring
- C-SSRS

11.7.19. Telephone contacts

Telephone calls will be made by a member of the research staff to the subject between scheduled study visits at Weeks 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27, 29, 30, 31, 33, 34, 35, 37, 38, 39, 41, 42, 43, 45, 46, 47, 49, 50 and 51. The telephone calls will be used to collect AEs and concomitant medications, as well as to remind subject about adherence to study drug administration and upcoming visits.

11.7.20. Unscheduled Visit for Dose Adjustment

If a dose increase or decrease is needed between regularly scheduled visits, the subject must return to the clinic for an unscheduled visit. The following procedures will be conducted during this visit for dose adjustment:

- Study drug accountability
- Dispense study drug
- AE monitoring
- Concomitant medication review

Other assessments are not required at such dose adjustment visits, but are permitted, based on the Investigator's judgment.

No dose decreases are allowed prior to Day 8.

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 informed consent form (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 the signing of the ICF to the last study visit (Visit 18 [Follow-up 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 changes from signing of the ICF in objective findings (eg, clinical laboratory value, ECG value, and physical examination observation), as determined by the Investigator, 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 and ECG tracings and over-read reports will be reviewed, signed and dated by the Investigator. The Investigator must determine the clinical significance of all out of range values for clinical laboratory tests and all abnormal ECG findings.

Any clinical laboratory value outside the normal range and any centrally over-read abnormal ECG finding will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether the value/finding is of clinical significance. Subjects with any clinically significant abnormal laboratory value(s) or ECG finding at Screening will not be allowed into the study (see Section 8.2). Retesting is allowed during the Screening Period and the retest used to determine eligibility after approval from the Medical Monitor; however, the Screening Period will not be extended to accommodate repeat laboratory / ECG tests unless repeat tests are needed due to a technical issue with laboratory sample processing, shipment or testing delay at the central laboratory. If a clinically significant laboratory or ECG abnormality is found after Screening, 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. Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Additional laboratory and ECG testing during the study may be performed if medically indicated.

12.3. Collection and Recording of Adverse Events

All AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All AEs that occur from the signing of the informed consent to the subject's last visit 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 that occur from the signing of the ICF up to the last visit must be recorded on the CRF and the data recorded should agree with that on the SAE form. In addition, pretreatment events that meet the definition of serious (Section 12.1.2) should be reported following the same guidelines.

Should the investigator become aware of an SAE greater than 30 days post last dose, the Investigator or an authorized delegate should report SAEs “spontaneously” to PPD-pharmacovigilance (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.

An initial or follow-up SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG immediately but no more than 24 hours after the Investigator or study center staff become aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor 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.

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 will be instructed to return to the study center within 48 hours of the first notification of pregnancy and undergo a serum 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).

If a pregnancy is reported for a study subject's partner from time of subject's first dose to 30 days post last dose, the subject's partner may be asked to sign a consent form to allow Sponsor to follow her pregnancy. The Sponsor's representative will provide instructions on how to collect pregnancy information in accordance with local requirements. Proper consent to collect the partner's information will be obtained before the collection of any information.

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG immediately but no more than 24 hours after the Investigator or study center staff becomes 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.

12.5. Data Monitoring Committee/Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will review safety data including data on AEs and SAEs approximately 3 times annually. The DSMB will be independent of the Sponsor, study CRO, and the Investigators and will be empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility. The DSMB may review blinded, unblinded, or partially unblinded data, but the Sponsor (with the exception of the relevant members of the pharmacovigilance team responsible for reporting Suspected Unexpected Serious Adverse Reactions [SUSARs]), study CRO, and the Investigators will remain blinded until the official unblinding of the database. The membership of the DSMB and its mandate will be described in a separate DSMB charter.

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

13.1. Criteria for Subject Termination

Subjects may be discontinued from study participation / the study drug at any time for any of the following reasons. The possible reasons for termination of study participation / study drug are as follows:

- Adverse event
- Lack of efficacy (specify; eg, no improvement in underlying condition)
- Lost to follow-up (specify)
- Withdrawal by subject (specify)
- Non-compliance with study drug (specify)
- Protocol deviation (specify)
- Death
- 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. Subjects discontinued from study drug will be discontinued from the study.

The reason 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.

Subjects who prematurely terminate the study participation will not be replaced.

13.2. Clinical Assessments after Study Drug Discontinuation

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

For subjects who have received study drug and prematurely discontinue from the study treatment (i.e., do not complete through Visit 17), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.7.17.

All subjects who discontinue from the study early will complete a follow up visit 7 (±2) days after the last dose of study drug as described in Section 11.7.18.

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 11.7.17 and safety Follow-up Visit as described in Section 11.7.18.

15. STATISTICS

15.1. Sample Size

A total of 300 subjects are expected to be enrolled from approximately 50 global sites, including the US and Europe. Subjects will be assigned randomly to receive SEP-363856 or active comparator in an allocation ratio of 2:1. The determination of sample size was based upon clinical considerations. The sample size of 300 subjects will provide approximately 80 subjects who are expected to complete 1 year of treatment with SEP-363856 to support sufficient long-term safety data on SEP-363856.

15.2. Analysis Populations

15.2.1. Safety Population

The safety population will consist of all subjects who were enrolled and receive at least one dose of study drug during the 52-week treatment period. The safety population will be used for the long-term safety and tolerability analyses. Subjects will be analyzed according to the actual treatment received.

15.2.2. Efficacy Population

The efficacy 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 population regardless of any protocol deviation. The efficacy population will be the primary population for the efficacy analyses. Subjects will be analyzed according to the treatment to which they are randomized.

15.2.3. Per Protocol Population

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

- Have 14 days or more overall exposure to study drug
- Have no important protocol deviations, determined by blinded data reviews prior to database lock

Selected efficacy endpoints will be analyzed using the PP population. Subjects will be analyzed according to the treatment to which they are randomized.

15.3. Data Analysis

15.3.1. Subject Disposition

Subject disposition will be summarized by the actual treatment group (if applicable) and overall for all subjects. The number and percent of subjects, who are screened, screen-failed, randomized, received study drug, and completed or discontinued early from the double-blind treatment period (including reasons for discontinuation) will be presented.

As exploratory analysis, the time-to-discontinuation (any reason) by treatment will be summarized descriptively and will also be tested with log-rank statistic and presented by a Kaplan-Meier plot.

15.3.2. Study Drug Exposure and Compliance

Duration of exposure and compliance will be summarized by treatment group for the safety population.

Duration of exposure (in days) will be calculated as: last dose date - first study dose date + 1. Duration of exposure will be summarized both as a continuous variable and categorically:

- Number and percentage of subjects with the study drug exposure ≥ 1, ≥ 14, ≥ 28, ≥ 42, ≥ 90, ≥ 120, ≥ 150, ≥ 180, ≥ 270, and ≥ 360 days;
- Number and percentage of subjects with the study drug exposure for 1 - 13, 14 - 27, 28 - 41, 42 - 89, 90 - 119, 120 - 149, 150 - 179, 180 - 269, 270 - 359, and ≥ 360 days

Percent compliance will be calculated overall for the treatment 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 treatment period. Subjects with missing compliance will not be classified as non-compliant. Percent compliance will be summarized both as a continuous variable and categorically (i.e. number and percentage of subjects in each compliance category: < 75%, 75% - 125%, > 125%, and missing).

Mean daily dose will be calculated for the treatment period as the cumulative dose (mg) of SEP-363856 or quetiapine XR (depending upon randomization) divided by the duration of exposure (in days), where cumulative dose is the sum of all doses a subject received during the treatment period. Modal daily dose will be determined as the daily dose that is taken for the most time (in terms of number of days) among all doses taken. Both mean daily dose and modal daily dose will be summarized.

15.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on blinded review of data listings. The IPD categories may include, but may not be limited to:

- Did not meet important inclusion and/or exclusion criteria.
- Received prohibited medication.
- Overall double-blind compliance rate < 75% or > 125%.

IPDs will be identified for all randomized subjects and presented in a data listing. The number and percentage of subjects within each IPD category will be summarized for the safety population.

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 each defined analysis population by treatment group and overall.

Medical and psychiatric history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 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

Efficacy data will be summarized descriptively by treatment for the efficacy population.

The observed values of PANSS total score and subscale scores (positive, negative, and general psychopathology), CGI-S score, BNSS total score, MADRS total score, BACS composite score, ESS total score, SLOF total and subscale scores, EQ-5D-5L VAS, index score and dimension score, UPSA-B total score, and MSQ score, at Baseline and each scheduled post-Baseline visit, will be summarized descriptively. Changes from Baseline in these efficacy measures as well as changes from baseline in tobacco use and cotinine concentrations, will be summarized at each scheduled post- Baseline visit.

PANSS total score and CGI-S score data will also be summarized by age, sex, race, number of prior hospitalizations for treatment of schizophrenia, duration of schizophrenia, geographic region, and country.

The proportion of subjects who achieve a response, defined as a 20% or greater improvement (i.e. decrease) in PANSS total score from the Baseline, will be calculated for each scheduled visit and the Week 52 last-observation-carried-forward (LOCF). The proportion of subjects who achieve a response, defined as a 30% or greater improvement (i.e. decrease) in PANSS total score from the Baseline, will be summarized similarly. As exploratory analyses, PANSS total score and subscale scores, CGI-S score, BNSS total score, and MADRS total score will be analyzed using a mixed model for repeated measures (MMRM) under the missing-at-random (MAR) assumption. Under this assumption, the efficacy outcome of subjects in each treatment group after early discontinuation will exhibit the same future evolution as subjects in the same group remaining in the study. The MMRM model will include fixed factors for treatment, visit as a categorical variable, country, and treatment-by-visit interaction, and include Baseline score as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. Kenward-Roger approximation will be used to calculate the denominator degrees of freedom. The main estimator of the efficacy estimand is the least squares (LS) mean difference in each score change from Baseline at Week 52 from the analysis model of observed repeated measures data.

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. These analyses will be based on the observed data only. Missing data will not be imputed.

Sensitivity analyses may be conducted to assess the impact of missing data on the PANSS total score and CGI-S score analysis results by deviating away from the MAR assumption; however, all efficacy analyses are exploratory in this safety study.

<u>Relapse</u>

Relapse will be identified programmatically and manual data review using the pre-defined criteria (specified below). The rate of relapse will be calculated as the proportion of subjects with

a relapse in the 52-week period out of the efficacy population, along with the 95% confidence interval. The time-to-relapse will be summarized descriptively and will also be presented by a Kaplan-Meier plot, with log rank test statistic.

Relapse will be defined as the earliest occurrence of any of the following:

- Worsening of > 30% PANSS total score from Baseline (Day 1) and a CGI-S score > 3.
- Hospitalization for worsening of psychosis.
- Emergence of suicidality, homicidality and/or risk of harm to self or others.
- Discontinuation from the study due to exacerbation of the underlying illness of schizophrenia.

The frequency of hospitalization due to relapse will be summarized descriptively by treatment.

15.3.6. Safety Analyses

15.3.6.1. Adverse Events

Both AEs and pre-treatment events will be coded using MedDRA.

The following summaries will be provided by treatment and by MedDRA SOC and PT:

- All AEs (including incidence rate and event count)
- AEs by severity (mild, moderate, severe; including incidence rate)
- AEs by relationship to study drug (related, not related; including incidence rate)

The following conventions will be followed in summarizing AEs:

- For incidence rate summaries, each subject will be counted only once within each SOC and within each PT.
- If a subject reports more than one AE within a PT and/or a SOC, the AE with the highest known severity will be used in the by severity summary. AEs with a missing severity will be assigned to the highest severity.
- For summaries by relationship to study drug, AEs will be grouped as “related” or “not related.” AEs assessed as “possible,” “probable,” or “definite,” will be grouped as “related.” AEs with a missing relationship to study drug will be regarded as related. If a subject reports more than one AE within the same SOC and PT, and any are related, the AE will be summarized as related.

Summaries of serious AEs (SAEs) and AEs leading to discontinuation by treatment will also be provided. All AEs starting after the last dose of the study drug up to 9 days following the last dose will be summarized separately. Data listings of AEs, SAEs, AEs leading to discontinuation, and deaths will be presented.

As exploratory analyses, the odds ratios (OR) with 95% confidence intervals (CI) of all AEs, SAEs, AEs leading to discontinuation, and AEs relating to extrapyramidal symptoms (EPS) between the two treatment groups will be provided.

15.3.6.2. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables and through by visit summaries of the observed values and the change from Baseline values by treatment. For parameters with categorical outcomes, the number and percentage of subjects with each outcome will be summarized by visit. The number and percentage of subjects with at least one potentially clinically significant (PCS) value post Baseline for selected parameters will also be presented. PCS criteria for clinical laboratory parameters will be provided in the SAP.

The change from Baseline values will be analyzed by nonparametric rank ANCOVA to compare between the SEP-363856 and quetiapine XR treatment groups for: lipid (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), glucose, HbA1c and prolactin levels. Details of the rank ANCOVA analysis will be provided in the SAP.

15.3.6.3. ECGs

ECG analysis will be based on the centrally read data. Observed values and changes from Baseline in ECG parameters will be summarized by treatment. In addition, the number and percentage of subjects with prolonged QTc intervals (> 450 msec, > 480 msec, and > 500 msec) and changes in QTc intervals ≥ 30 but < 60 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 will be summarized by presenting by visit summaries of the observed 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 quetiapine XR treatment groups. In addition, the number and percentage of subjects with at least one PCS value post Baseline for selected parameters will be presented. PCS criteria for the vital sign parameters will be provided in the SAP.

Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after a subject has been standing for at least 2 to 4 minutes, compared to the systolic blood pressure and diastolic pressure measured in the supine position, respectively. Orthostatic tachycardia is defined as a pulse rate increase of ≥ 20 bpm and a pulse rate of > 100 bpm after a subject has been standing for at least 2 to 4 minutes, compared to the pulse rate measured in the supine position.

The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized for Baseline and the overall post-Baseline period, as well as by visit.

15.3.6.5. Physical and Neurological Examination

Any clinically significant physical and neurological examination findings at screening will be captured as medical history and summarized together with the other medical history data. Clinically significant new findings or 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 Anatomical Therapeutic Chemical (ATC) 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/time on or after the first dose of study drug and on or before the last dose of study drug; or with a start date/time prior to, and an end date/time on or after, the first dose of study drug, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the first dose of study drug will be considered prior medications. Medications that started after 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 the overall post-Baseline period and by visit.

15.3.6.8. Movement Disorder Measures

Movement disorder measures include SAS, BARS and AIMS. The observed values of SAS mean score, BARS total score and AIMS total score at Baseline and each scheduled post-Baseline visit will be summarized by treatment. Changes from Baseline in these measures will also be summarized for each scheduled post-Baseline visit by treatment. BARS total score and AIMS total score will each be analyzed using an ANCOVA model which includes factors for treatment and country, and the respective Baseline score as the covariate. Additional analyses on the movement disorder scales will be described in the SAP.

15.3.6.9. Healthcare Resource Utilization

The frequency and percentage of subjects with physician's office visits, ER visits and hospitalizations (overall and those related to schizophrenia) in the past 3 months of each visit will be summarized. Employment status for the past 3 months, length of hospital stays and the average number of hours a caregiver(s) spends helping the subject per week will be summarized using descriptive statistics.

15.3.6.10. Subgroup Analysis

Selected safety data will be summarized by subgroups of geographic region, sex, age, race, number of prior hospitalizations for treatment of schizophrenia, and duration of schizophrenia. Details of subgroup analysis of the safety data will be provided in SAP.

CCI

CCI

[redacted]

15.3.9. Interim Analysis

A Data and Safety Monitoring Board (DSMB) will review safety data approximately 3 times annually during the study. The DSMB will be independent of the Sponsor, study contract research organization (CRO) and the Investigators and will be empowered to recommend stopping the study due to safety concerns. The membership of the DSMB and its mandate will be described in a separate DSMB Charter. Statistical analysis plan for the DSMB reviews will be specified in an DSMB Statistical Analysis Plan.

No other interim analysis is planned.

15.3.10. Treatment of Missing Data

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

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, ECG results, POP PK, CCI [redacted] and some scales), will be recorded in the subject's electronic CRF. Data will be entered into source documents prior to being transcribed into the CRF. 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.

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 6: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type
Obtain informed consent	A
CCI [redacted]	
Review inclusion/exclusion criteria	A
Prior/concomitant medication review	A
Dispense study drug	E
Study drug accountability	A, E
Demography	A
Medical history	A
Psychiatric history	A
Tobacco use information	A
SCID-CT	None
Physical and neurological examination	A
Vital signs	A
Weight (including BMI)	A
Height	A
Waist circumference	A
12-Lead ECG	C
Hematology, chemistry, and urinalysis	B
Serum FSH	B
Serum β-hCG, females of childbearing potential	B
CCI [redacted]	

Table 6: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type
CCI	
Plasma cotinine level	D
Urine drug screen	B
Urine β-hCG, females only	A
Positive and Negative Syndrome Scale (PANSS)	F
Clinical Global Impression – Severity (CGI-S)	F
Brief Negative Symptom Scale (BNSS)	F
Montgomery-Asberg Depression Rating Scale (MADRS)	F
Columbia Suicide Severity Rating Scale (C-SSRS)	A
Simpson-Angus Scale (SAS)	F
Barnes Akathisia Rating Scale (BARS)	F
Abnormal Involuntary Movement Scale (AIMS)	F
ESS	F
BACS	G
SLOF	F
EuroQol-5D-5L	F
MSQ	F
Healthcare resource utilization	A
UPSA-B	A
Adverse event (AE) monitoring	A
Statistical analysis	SAS®, version 9.2 or higher

A = EDC (Medidata Rave); B = Central lab; C = ECG central vendor; D = LIMS/ASCII; E = IWRS; F = WCG MedAvante-ProPhase; G = VeraSci.

Abbreviations: EDC = electronic data capture; CDR = clinical data repository; ePRO = electronic patient reported outcomes; IWRS = interactive web response system; LIMS = laboratory information management system.

16.3. Study Monitoring

This study will be monitored using a risk-based approach 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 International Council for Harmonization (ICH) Good Clinical Practice (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 center facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center 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 handwritten or computer-generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, e.g., 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, e.g., 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 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.

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.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license, where applicable) and financial disclosure information. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on curriculum vitae.
- Appropriate diploma number stated on curriculum vitae.
- Copy of the diploma.

The Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to Sponsor/CRO.

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 subject's 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, 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 15 years (or at least 25 years if the EU) 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. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.9. 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, SEP361-304, Version 3.00 "A Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Long-term Safety and Tolerability of SEP-363856 in 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

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 at least 5 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. 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, Red Blood cell (RBC) Count, White blood cell (WBC) - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Cholesterol, Creatinine, Creatinine clearance (calculated GFR, not calculated at Week 1), Creatinine phosphokinase (CPK), Free T3, Free T4, HDL-Cholesterol, hs C-reactive Protein (CRP), Glucose, Hemoglobin A1c (HbA1c), LDL-Cholesterol, Magnesium (Mg), Phosphorus (P), Potassium (K), Prolactin, Protein (Total), Serum Insulin, Sodium (Na), Thyroid stimulating hormone (TSH), Triglycerides, Uric Acid

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

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

SEROLOGY PANEL: Hepatitis B Ag, Hepatitis C Ab

OTHER TESTS: Serum Pregnancy (β-HcG) (in female subjects only), Urine Pregnancy Test (in female subjects only), Follicle stimulating hormone (in female subjects with suspected menopause).

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 until the test(s) has (have) normalised or stabilised.

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