SEP-363856

Clinical Study Protocol SEP361-308

An 8-Week, Open-Label Study Evaluating the Effectiveness, Safety and Tolerability of SEP-363856 in Subjects with Schizophrenia Switched from Typical or Atypical Antipsychotic Agents

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	PPD , MD PPD , Head of Global Clinical Research, Psychiatry Sumitomo Pharma America, Inc.	Mobile: PPD Email: PPD
Medical Monitor	PPD , MD PPD IQVIA	Phone: PPD Toll free number: PPD Email: PPD
SAE/Pregnancy Reporting	PPD Pharmacovigilance (PVG)	Fax: CCI Email: CCI

1. SYNOPSIS

Name of Sponsor/Company: Sumitomo Pharma America, Inc.

Name of Investigational Product: SEP-363856

Name of Active Ingredient: SEP-363856-01 (hydrochloride salt)

Title of Study: An 8-Week, Open-Label Study Evaluating the Effectiveness, Safety and Tolerability of SEP-363856 in Subjects with Schizophrenia Switched from Typical or Atypical Antipsychotic Agents

Proposed Indication: Schizophrenia

Study Centers: Approximately 24 sites in North America

Phase of Development: 3

Study Objectives:

Primary:

- To evaluate the safety and effectiveness of switching clinically stable outpatients with schizophrenia from a typical or atypical antipsychotic to SEP-363856 over a period of 8 weeks as assessed by the percentage of subjects who discontinue from the study due to an adverse event or lack of efficacy

Secondary:

- To evaluate the safety and effectiveness of switching clinically stable outpatients with schizophrenia from a typical or atypical antipsychotic to SEP-363856 over a period of 8 weeks as assessed by the percentage of subjects who discontinue for any reason (ie, all causes of discontinuation)

Other:

- To evaluate the tolerability and safety of switching clinically stable outpatients with schizophrenia from a typical or atypical antipsychotic to SEP-363856 over a period of 8 weeks using:
  - Adverse event reports
  - Clinical laboratory tests
  - Vital sign measurements
  - 12-lead electrocardiograms (ECG)
  - Columbia – Suicide Severity Rating Scale (C-SSRS)
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)
  - Simpson-Angus Scale (SAS)
- To evaluate the effectiveness of SEP-363856 using:
  - Positive and Negative Syndrome Scale (PANSS)
  - Clinical Global Impression-Severity (CGI-S) scale
  - Clinical Global Impression-Improvement (CGI-I) scale
  - Brief Negative Symptom Scale (BNSS)
- To evaluate the effects of SEP-363856 on health-related quality of life as measured by the Short Form Health Survey (SF-12)

- To evaluate the effects of SEP-363856 on functional capacity as measured by the Personal and Social Performance Scale (PSP)
- To evaluate medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ)
- To evaluate sleep as measured by the Pittsburgh Sleep Quality Index (PSQI)
- To evaluate the impact of SEP-363856 on healthcare resource utilization (HCRU)

Study Design:

This is an 8-week, outpatient, multicenter, open-label, single-group, flexible-dose study designed to evaluate the safety and tolerability, as well as effectiveness of switching clinically stable adult subjects with schizophrenia from a typical or atypical antipsychotic to SEP-363856. This study is projected to enroll approximately 120 subjects into a single treatment group (SEP-363856). Over the 8-week treatment period, subjects will receive flexibly dosed SEP-363856 (50 to 100 mg/day) and the Investigator will have the discretion to discontinue each subject's pre-switch antipsychotic treatment by the end of Week 2, 3, 4, 5, or 6. Appropriate duration of pre-switch antipsychotic taper for individual subjects will be provided as in Section 21 Appendix II.

Once the pre-switch antipsychotic has been fully discontinued, subjects will continue to receive SEP-363856 flexible 50 to 100 mg/day until study endpoint, at the end of Week 8. Study drug will be taken at the same time each evening at bedtime and can be taken with or without food.

The study will consist of three periods: Screening/Washout (up to 21 days), Treatment (8 weeks) and a Follow-up visit (7 ± 2 days after the last dose of study drug for those subjects who discontinue prior to the Week 8 visit or who complete the study but do not enroll in the open-label extension study SEP361-309) as shown in Figure 1. Overall study design details provided in Section 7.1 and Table 2 schedule of assessments.

Number of Subjects (planned): 120

Diagnosis and Key Criteria for Subject Inclusion:

Section 8 of the full protocol includes the complete list of inclusion and exclusion criteria.

Key Inclusion criteria (not all inclusive):

- Male or female subject between 18 to 65 years of age (inclusive) at the time of consent.
- Subject meets Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria for a diagnosis of schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID-5-CT]). The time since the subject's diagnosis must be ≥ 1 year prior to Screening. Every attempt should be made to obtain medical records or to have correspondence with a previous or current treating provider for the purposes of confirming that the previous course and treatment is consistent with schizophrenia.
- 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 (ie, no evidence of an acute exacerbation of schizophrenia) by the Investigator for at least 8 weeks prior to Baseline.
- Subject must not have been hospitalized for psychiatric illness for at least 8 weeks prior to Screening.
- Subject must be judged by the Investigator to be an appropriate candidate for switching current antipsychotic medication due to safety or tolerability concerns and/or insufficient efficacy.

Investigational Product, Dosage and Mode of Administration:

SEP-363856 tablets (50 mg, 75 mg, or 100 mg) will be utilized. SEP-363856 will be administered orally once daily. SEP-363856 will be taken at the same time each evening at bedtime and may be taken without regard for food.

Duration of Treatment: 8 weeks

Reference Therapy, Dosage and Mode of Administration: Not applicable

Prior and Concomitant Medications:

Subjects will remain on their pre-switch antipsychotic and switch to SEP-363856 as described in Section 7.1. Subjects who enter Screening on two antipsychotic medications must washout of their secondary antipsychotic prior to Baseline (see Section 8.1 Inclusion criterion 12). Subjects are permitted to remain on non-prohibited psychotropic medications other than the primary pre-switch antipsychotic or secondary antipsychotic, that have been part of their ongoing treatment regimen. Except for medications listed in Section 10.3.4, the psychotropic medication must have been stable for at least 6 weeks prior to Screening and will be maintained at a stable dose and regimen throughout study participation (see Section 10.3.1 for psychotropic medication adjustments).

Allowable concomitant psychotropic medications are described in Section 10.3.4. Treatment with sedative hypnotics is permitted during the Screening/Washout Period but should be tapered as clinically appropriate prior to receiving SEP-363856. This is to conform with and adequately prepare the subject for the protocol-specified limitations applicable to these agents.

Medications used to treat extrapyramidal symptoms (EPS) should not be given prophylactically. They are to be tapered and discontinued while the pre-switch antipsychotic is being tapered in a manner that is consistent with labeling recommendations and conventional medical practice. These medications may be reinstated, after consultation with the Medical Monitor, if EPS or akathisia symptoms emerge after treatment discontinuation.

See Section 10.3 for further information on prior and concomitant medications.

Study Endpoints:

Primary Endpoint:

- Percentage of subjects who discontinue for clinical reasons (ie, discontinued due to an adverse event [AE] or lack of efficacy)

Secondary Endpoint:

- Percentage of subjects who discontinue for any reason (ie, all causes for discontinuation)

Other Endpoints:

- The incidence of overall AEs, serious adverse events [SAEs], and AEs leading to discontinuation
- Observed values and changes from Baseline in clinical laboratory tests (hematology, chemistry and urinalysis) (Section 23 Appendix IV)
- Observed values and changes from Baseline in vital signs (including body weight, body mass index [BMI], waist circumference, temperature, blood pressure [supine and standing], heart rate [supine and standing] and respiratory rate)
- Observed values and changes from Baseline in 12-lead ECG parameters
- Frequency of subjects with suicidal ideation and suicidal behavior based on the C-SSRS
- Changes from Baseline in BARS, AIMS and SAS scores
- Changes from Baseline to Week 8 in:

- PANSS total score and subscale scores (positive, negative, and general psychopathology)
- PANSS Marder Factor (five-factor) scores (positive, disorganized, negative, hostility, and depression/anxiety), and Uncorrelated PANSS Score Matrix (UPSM)
- CGI-S score
- BNSS total score
- SF-12 scores
- PSP total score
- MSQ score
- PSQI global score

- CGI-I score at Week 8
- HCRU (including numbers of physician office visits, emergency room (ER) visits and hospitalizations, length of hospital stays, employment status and average number of hours caregiver(s) spends helping subjects per week.)
- Nicotine use at baseline and Week 8 (end of treatment [EOT]/early termination [ET])

Statistical Methods:

The analysis of safety and tolerability, and functionality will be based on the safety population, which includes all subjects who receive at least one dose of study drug during the 8-week Treatment Period. The analysis of effectiveness will be based on the effectiveness population, which consists of all subjects who are enrolled, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline effectiveness measurement in PANSS or CGI-S.

Percentage of subjects who discontinue for clinical reasons, ie, due to adverse event or lack of efficacy, will be summarized by presenting the number and percentage of subjects who drop out of the study for each reason. In addition, the subset of subjects who discontinue due to an AE indicative of worsening schizophrenic illness will be tabulated separately.

Percentage of subjects who discontinue for any reason (ie, “all cause discontinuation”) will be summarized by presenting the number and percentage of subjects who drop out of the study for each reason.

AEs, AEs leading to discontinuation, and serious AEs will be summarized by presenting 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 (including 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. The frequency of subjects with suicidal ideation and suicidal behavior based on the C-SSRS will be provided.

Measures of motor function will be assessed using the SAS, BARS, and AIMS scales. Mean changes from Baseline in these measures by scheduled visit will be presented.

Descriptive statistics will be presented on the change from Baseline to Week 8 in PANSS total score and subscale scores, CGI-S score, BNSS total score, PSP total score, PSQI global score, SF-12 score, and MSQ score. For CGI-I score, descriptive statistics by visit, including Week 8, will be presented.

Descriptive statistics by visit will be presented for the HCRU. The frequency and percentage of subjects with physician office visits, ER visits, hospitalizations at Baseline and at each post-Baseline

scheduled visit will be summarized. The change in the number of physician's office visits, ER visits, and hospitalizations per month, the average length of hospital stays, and the average number of hours a caregiver spends per week helping the subject from Baseline at each post-Baseline scheduled visit will be summarized.

Subgroup analyses will be described in the statistical analysis plan (SAP).

Sample Size:

Approximately 120 subjects will be required for this study. This sample size was determined by the width of the 95% confidence interval for the proportion of subjects who may discontinue due to clinical reasons by Week 8 to ensure the precision of the estimate of the true discontinuation treatment failure rate due to clinical reasons. Assuming 1) 15% of SEP-363856 treated subjects will experience discontinuation due to clinical reasons by Week 8 and 2) 6.4% as the half width (the distance between the upper/lower limits to the point estimate) of the 95% confidence interval (ie, [8.6%, 21.4%]), approximately 120 subjects will be required.

Table 2: Schedule of Assessments

	Screening Period	Treatment Period									Follow-up Period
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screening[a]	Pre-switch Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7 TC	Week 8[b] EOT/ET[c]	Week 9[d] Follow-up
Study Day [e]	Days -21 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	7 ± 2 days after last dose
Informed consent	X										
Informed consent for duplicate subject check	X										
CCI											
Review inclusion/exclusion criteria	X	X									
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Dispensation of study drug[g]		X	X	X	X	X	X	X			
Study drug accountability			X	X	X	X	X	X		X	
Demography	X										
Medical history	X										
Psychiatric history	X										
Nicotine use information	X									X	
SCID-5-CT[h]	X										
Physical and neurological examination	X									X	X
Height	X										
Vital signs[i]	X	X	X	X	X	X	X	X		X	X
Weight (including BMI)[j]	X	X				X				X	
Waist circumference		X				X				X	
12-lead Electrocardiogram (ECG)	X	X								X	
Hematology, chemistry, and urinalysis[k]	X	X								X	
Blood sample for hepatitis screening	X										

Table 2: Schedule of Assessments (Continued)

	Screening Period	Treatment Period									Follow-up Period
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screening[a]	Pre-switch Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7 TC	Week 8[b] EOT/ET[c]	Week 9[d] Follow-up
Study Day [e]	Days -21 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	7 ± 2 days after last dose
Serum follicle stimulating hormone (FSH)[l]	X										
Serum human chorionic gonadotropin (β-hCG), (females)	X									X	
Urine β-hCG (females)[m]		X				X					X
Rapid urine β-hCG (females)[m]										X	
CCI											
Blood sample for POPPK[o]		X	X			X				X	
Urine drug screen[p]	X	X				X				X	
Rapid urine drug screen [p]										X	
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X		X		X		X	
Clinical Global Impression – Severity (CGI-S)	X	X	X	X		X		X		X	
Clinical Global Impression – Improvement (CGI-I)			X	X		X		X		X	
Brief Negative Symptom Scale (BNSS)		X				X				X	
Pittsburgh Sleep Quality Index (PSQI)		X				X				X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS)[q]		X								X	
Barnes Akathisia Rating Scale (BARS)[q]		X								X	

Table 2: Schedule of Assessments (Continued)

	Screening Period	Treatment Period									Follow-up Period
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screening[a]	Pre-switch Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7 TC	Week 8[b] EOT/ET[c]	Week 9[d] Follow-up
Study Day [e]	Days -21 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	7 ± 2 days after last dose
Abnormal Involuntary Movement Scale (AIMS)[q]		X								X	
SF-12		X								X	
Medication Satisfaction Questionnaire (MSQ)		X								X	
Personal and Social Performance Scale (PSP)		X								X	
Healthcare Resource Utilization (HCRU)[r]		X								X	
Pretreatment/Adverse events (AE) monitoring[s]	X	X	X	X	X	X	X	X	X	X	X
Duplicate Subject Check[t]	X									X	
Tokenization consent (optional) [f]	X										

Abbreviations: AE = adverse event; BARS = Barnes Akathisia Rating Scale; β hCG = human chorionic gonadotropin; BMI = Body Mass Index; BNSS = Brief" Negative Symptom Scale; C-SSRS = Columbia Suicide Severity Rating Scale; eCRF = electronic case report form; EDC = electronic data capture; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; EOT = end of treatment; ET = early termination; FSH = Follicle stimulating hormone; MSQ = Medication Satisfaction Questionnaire; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; PK = pharmacokinetic; PSQI = Pittsburgh Sleep Quality Index; SAS = Simpson-Angus Scale; SCID-5-CT = Structured Clinical Interview for DSM-5; SF-12 = Short Form Health survey; Clinical Trials Version; TC = telephone contact visit; UDS = urine drug screen.

[a.] Subjects who screen fail can be re-screened up to 2 times 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.

[b.] All procedures and assessments scheduled for Week 8 will be utilized as Baseline procedures and assessments for the open-label extension study (SEP361-309).

[c.] 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.

[d.] Subjects who discontinue early from the study or complete the study and do not enter the extension study (SEP361-309) 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, administration of C-SSRS, and collection of AEs, and concomitant medications may occur by telephone contact if the subject is unable to come to the clinic for the Follow-up Visit.

[e.] Visit window for Day 8 is +2 days and visit windows post Day 8 are ± 2 days for every Visit.

[f.] Requested, but not required for study participation.

g. All study drug will be taken once daily in the evening at bedtime by mouth, without regard to food.
h. The SCID-5-CT will be used to support the DSM-5 diagnosis and must be administered by a qualified rater with at least 2 years' experience with the population under study.
i. Vital signs will include respiratory rate, oral body temperature and supine and standing measurements of blood pressure and pulse rate.
j. BMI will be calculated and recorded in the eCRF by 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) at Pre-switch Baseline (Visit 2) and Week 8/EOT/ET (Visit 10). Fasting for 8 hours prior to Screening (Visit 1) is also recommended to avoid potential retests. Blood samples should be drawn in the morning followed by a snack or meal. A list of clinical laboratory tests is provided in Section 23.
l. Blood samples for follicle stimulating hormone (FSH) will be collected for post-menopausal women or if menopause is suspected.
m. Any positive urine β-hCG test should be confirmed by a serum β-hCG test.
[redacted]
o. Blood samples for determination of plasma SEP-363856 concentrations will be collected predose (prior to administration of the first dose) on Day 1; 3 additional samples will be collected on Days 8, 29 and 57/ET. The time and date of the previous dose of study drug and the time and date of blood sampling must be recorded. The remaining plasma samples, after PK measurement is completed, CCI [redacted].
p. Positive urine drug screen (UDS) results should be discussed with the Medical Monitor.
q. Unscheduled SAS, BARS and AIMS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment.
r. Healthcare resource utilization questions are described in Section 11.5.8. Baseline will have 3-month lookback period. Week 8/ET will be since last assessment.
s. Events occurring prior to first dose of study drug are pretreatment events. Events occurring after first dose of study drug are adverse events. Determination done programmatically.
t. Where local regulations allow, duplicate subject check will be performed. Following the last contact with a subject, the duplicate enrollment system should be updated, as appropriate.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: List of Abbreviations

Abbreviation	Full Form
5-HT	5-Hydroxytryptamine (serotonin)
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
β-hCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
BNSS	Brief Negative Symptom Scale
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia – Suicide Severity Rating Scale
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	Electroencephalogram
EOT	End of Treatment
EPS	Extrapyramidal Symptoms
ET	Early Termination
ER	Emergency Room
FDA	U.S. Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCRU	Healthcare Resource Utilization
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPD	Important Protocol Deviation
IRB	Institutional Review Board
LC-MS/MS	Liquid chromatography-tandem mass spectrometry method for determining plasma concentrations
LIMS	Laboratory Information Management System
LOCF	Last Observation Carried Forward
MAOIs	Monoamine Oxidase Inhibitors
MCS-12	Mental Component Summary of the SF-12
MedDRA	Medical Dictionary for Regulatory Activities
MSQ	Medication Satisfaction Questionnaire
MTD	Maximum Tolerated Dose

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
OLE	Open Label Extension
PANSS	Positive And Negative Syndrome Scale
PCS	Potentially Clinically Significant
PCS-12	Physical Component Summary of the SF-12
PD	Pharmacodynamic(s)
PE	Physical Examination
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
POPPK	Population Pharmacokinetics
PPD-PVG	CRO acting on Sunovion's behalf for Pharmacovigilance activities
PR interval	Time between P wave and QRS in electrocardiography
PS	Pre-Switch
PSP	Personal and Social Performance Scale
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
PVG	Pharmacovigilance
QRS interval	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
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
REM	Rapid Eye Movement
RR interval	Distance between two consecutive R waves
RTSM	Randomization and Trial Supply Management system
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SF-12	Short Form Health Survey

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
SOC	System Organ Class
SOP	Standard Operating Procedure
TAAR1	Trace Amine Associated 1 Receptors
UDS	Urine Drug Screen
UPSM	Uncorrelated PANSS Score Matrix
US, USA	United States, United States of America
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 dosed.
Study Drug (or Study medication)	Term to cover investigational drug.
Treatment Period	The period of the study in which the study drug is administered.
Completed Subject	Any subject who participated throughout the duration of the Treatment Period, up to and including Week 8.
Early Termination Subject	Any subject who was successfully screened and was dosed 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 neurodegenerative disorder characterized by a mixture of positive symptoms (eg, hallucinations, delusions, and disordered thought), 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). Despite scientific advances, schizophrenia remains one of the most challenging diseases to treat due to its variable nature, the heterogeneity of clinical response, and the side effects associated with current treatments. New treatments with greater efficacy and tolerability are needed to reduce the associated high rates of morbidity and mortality (Lehman-2004; Tandon-2008).

The patient population with schizophrenia is estimated to be about 2.2 million in the United States (US) and 51 million worldwide, with an incidence of 100,000 patients/year in the US and 1.5 million patients worldwide (Schizophrenia Statistics 2022). Schizophrenia is believed to be caused by a combination of genetic and environmental factors (Minzenberg-2008), and dopaminergic, serotonergic, and glutamatergic systems are believed to play a role in the disease pathology and symptomatology (Kuroki-2008; Kim-2009). Presently available treatments are only partially effective in alleviating acute and chronic symptoms.

The current standard of care for the treatment of schizophrenia is the use of second generation antipsychotics or “atypical antipsychotics” (Lehman-2004; Kreyenbuhl-2009; Meltzer-2011; Nakamura-2009). These “atypicals” are thought to have fewer extrapyramidal side effects compared to first generation antipsychotics or “typical antipsychotics” (eg, haloperidol) (Leucht-2009; Naber-2009). However, some patients respond poorly to both atypical and typical antipsychotics, and some continue to have symptoms and substantial functional/cognitive impairment (Keefe-2006; Webber-2008). Very few patients return to baseline (pre-psychosis) function (Schultz-1999; Pearlson-2000; Kapur-2001). In addition, some atypical agents 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 comorbid medical problems as well as contribute to poor compliance and treatment discontinuation.

The large-scale NIMH-CATIE schizophrenia study found that 70% to 80% of outpatients discontinue medications before 18 months because of lack of efficacy or occurrence of side effects (Lieberman-2005). Noncompliance often leads to relapse of symptoms and the need for rehospitalization (Ascher-Svanum-2010; Munro-2011; Morken-2008). Clearly, an unmet need exists for new, effective, 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 (ie. positive and negative symptoms), cognition, and depression. The molecular target responsible for the therapeutic profile of SEP-363856 has not been completely elucidated, but it does not act on dopamine D2 receptors and it has agonist activity at trace amine–associated receptor 1 (TAAR1) and 5-hydroxytryptamine type 1A (5-HT1A)

receptors, which suggests SEP-363856 may represent a new class of psychotropic agent for the treatment of psychosis in schizophrenia (Koblan-2020; Dedic-2021).

SEP-363856 has shown broad efficacy in animal models of schizophrenia (Dedic-2019). Rat electroencephalogram (EEG) studies showed that SEP-363856 suppressed rapid eye movement (REM) sleep in a dose dependent manner. In nonhuman primate functional magnetic resonance imaging (fMRI) experiments, similar to risperidone, pretreatment with SEP-363856 also reduced the ketamine brain fMRI response in rhesus monkey supporting an antipsychotic-like profile.

As of 24 September 2021, in clinical studies, a total of 914 adult subjects have received oral doses of SEP-363856 in 16 completed and 6 ongoing studies. A total of 657 adult subjects received oral doses of SEP-363856 in completed and ongoing studies in subjects with schizophrenia. SEP-363856 demonstrated statistically significant efficacy and overall safety and tolerability compared to placebo in a Phase 2 clinical trial, SEP361-201, in acutely ill adults with schizophrenia (Koblan-2020) and in a long-term open-label extension, SEP361-202 (Correll-2021). Additional acute and long-term Phase 3 studies of acute schizophrenia are underway.

Switching between antipsychotic medications is common in the treatment of schizophrenia (Faries-2009). There may be many reasons for switching antipsychotic treatment, including unsatisfactory response to current treatment, poor tolerability, comorbid physical and psychiatric conditions, and patient request. Clinically warranted switches can provide benefits by enhancing treatment effectiveness, tolerability, and overall acceptance by patients (Weiden-2003). Studies have shown that up to one-third of outpatients with schizophrenia in the United States switch antipsychotic therapy within one year (Weiden-2006, Buckley-2007). According to most empirically based criteria (Kinon-2000), successful switching paradigms involve gradual discontinuation of the original antipsychotic drug upon initiation of the new treatment. Individual patient characteristics, as well as the binding profile and dose level of the original antipsychotic, can influence the appropriate duration for successful discontinuation (Buckley-2007; Cerovecki-2013; Takeuchi-2018).

In light of the novel mechanism of action of SEP-363856, it is important to understand the safety and effectiveness by which a patient can be switched to SEP-363856 using common methods employed in a clinical outpatient setting.

Therefore, the current study is an 8-week, outpatient, multicenter, flexible-dose, single-group study designed to evaluate safety and tolerability as well as effectiveness of switching clinically stable outpatients with schizophrenia, who can potentially benefit from a switch for tolerability or efficacy reasons, from their pre-switch antipsychotic medication to SEP-363856.

4.3. Risk-Benefit Assessment

In an adequate and well-controlled 4-week Phase 2 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.

Coadministration of SEP-363856 with other antipsychotic drugs during a 2 to 6-week cross taper has not been fully elucidated.

Hypotension / orthostatic hypotension and syncope are potential risks associated with administration of SEP-363856 to subjects with schizophrenia. In general, events of hypotension / orthostatic hypotension experienced by the schizophrenia population have been transient, mild or moderate in severity, non-serious, infrequently led to discontinuation of study drug, and did not require concomitant treatment or intervention. In general, events of syncope experienced by subjects with schizophrenia have been self-limiting, non-serious, transient (duration of the associated loss of consciousness [when reported] ranged between 10-20 seconds), moderate in intensity, did not lead to discontinuation of study drug, and did not require concomitant treatment or intervention.

5. STUDY OBJECTIVES

5.1. Primary Objective

- To evaluate the safety and effectiveness of switching clinically stable outpatients with schizophrenia from a typical or atypical antipsychotic to SEP-363856 over a period of 8 weeks as assessed by the percentage of subjects who discontinue from the study due to an adverse event or lack of efficacy

5.2. Secondary Objective

- To evaluate the safety and effectiveness of switching clinically stable outpatients with schizophrenia from a typical or atypical antipsychotic to SEP-363856 over a period of 8 weeks as assessed by the percentage of subjects who discontinue for any reason (ie, all causes of discontinuation)

5.3. Other Objectives

- To evaluate the tolerability and safety of switching clinically stable outpatients with schizophrenia from a typical or atypical antipsychotic to SEP-363856 over a period of 8 weeks using:
  - Adverse event reports
  - Clinical laboratory tests
  - Vital sign measurements
  - 12-lead electrocardiograms (ECG)
  - Columbia – Suicide Severity Rating Scale (C-SSRS)
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)
  - Simpson-Angus Scale (SAS)
- To evaluate the effectiveness of SEP-363856 using:
  - Positive and Negative Syndrome Scale (PANSS)
  - Clinical Global Impression-Severity (CGI-S) scale
  - Clinical Global Impression-Improvement (CGI-I) scale
  - Brief Negative Symptom Scale (BNSS)
- To evaluate the effects of SEP-363856 on health-related quality of life as measured by the Short Form Health Survey (SF-12)
- To evaluate the effects of SEP-363856 on functional capacity as measured by the Personal and Social Performance Scale (PSP)
- To evaluate medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ)
- To evaluate sleep as measured by the Pittsburgh Sleep Quality Index (PSQI)
- To evaluate the impact of SEP-363856 on healthcare resource utilization (HCRU)

6. STUDY ENDPOINTS

6.1. Primary Endpoint

- Percentage of subjects who discontinue for clinical reasons (ie, discontinued due to an adverse event [AE] or lack of efficacy)

6.2. Secondary Endpoint

- Percentage of subjects who discontinue for any reason (ie, all causes for discontinuation)

6.3. Other Endpoints

- The incidence of overall AEs, serious adverse events [SAE]s, and AEs leading to discontinuation
- Observed values and changes from Baseline in clinical laboratory tests (hematology, chemistry and urinalysis) (Section 23 Appendix IV)
- Observed values and changes from Baseline in vital signs (including body weight, body mass index [BMI], waist circumference, temperature, blood pressure [supine and standing], heart rate [supine and standing] and respiratory rate)
- Observed values and changes from Baseline in 12-lead ECG parameters
- Frequency of subjects with suicidal ideation and suicidal behavior based on the C-SSRS
- Changes from Baseline in BARS, AIMS and SAS scores
- Changes from Baseline to Week 8 in:
  - PANSS total score and subscale scores (positive, negative, and general psychopathology)
  - PANSS Marder Factor (five-factor) scores (positive, disorganized, negative, hostility, and depression/anxiety), and Uncorrelated PANSS Score Matrix (UPSM)
  - CGI-S score
  - BNSS total score
  - SF-12 scores
  - PSP total score
  - MSQ score
  - PSQI global score
- CGI-I score at Week 8

- HCRU (including numbers of physician office visits, emergency room [ER] visits and hospitalizations, length of hospital stays, employment status and average number of hours caregiver(s) spends helping subjects per week.)
- Nicotine use at baseline and Week 8 (end of treatment [EOT]/early termination [ET])

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

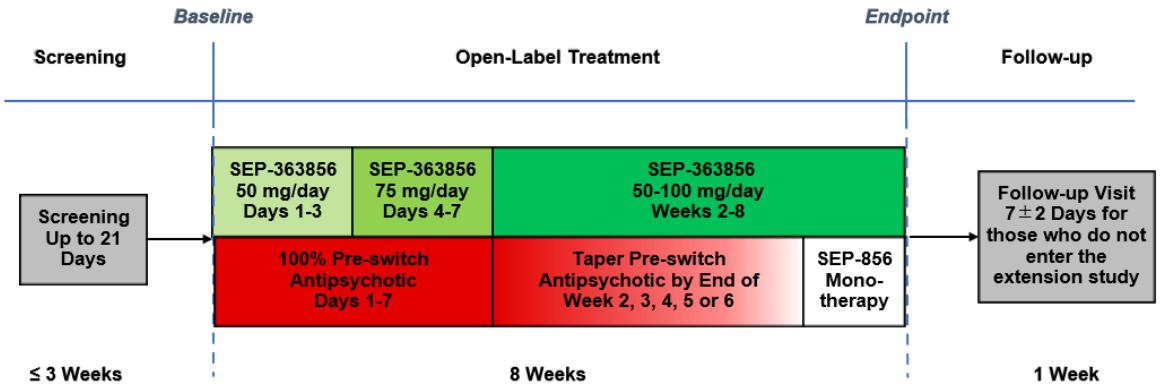
This is an 8-week, outpatient, multicenter, open-label, single-group, flexible-dose study designed to evaluate the safety and tolerability, as well as effectiveness of switching clinically stable adult subjects with schizophrenia from a typical or atypical antipsychotic to SEP-363856. This study is projected to enroll approximately 120 subjects into a single treatment group (SEP-363856). Over the 8-week treatment period, subjects will receive flexibly dosed SEP-363856 (50 to 100 mg/day) and the Investigator will have the discretion to discontinue each subject's pre-switch antipsychotic treatment by the end of Week 2, 3, 4, 5, or 6. Appropriate duration of pre-switch antipsychotic taper for individual subjects will be provided as in Section 21 Appendix II.

Once the pre-switch antipsychotic has been fully discontinued, subjects will continue to receive SEP-363856 flexible 50 to 100 mg/day until study endpoint, at the end of Week 8. Study drug will be taken at the same time each evening at bedtime and can be taken with or without food.

The study will consist of three periods: Screening/Washout (up to 21 days), Treatment (8 weeks) and a Follow-up visit (7 ± 2 days after the last dose of study drug for those subjects who discontinue prior to the Week 8 visit or who complete the study but do not enroll in the open-label extension study SEP361-309).

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in, Table 2 Schedule of Assessments, and Section 11.9, Study Visits and Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic



Screening 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 Period of up to 21 days, during which they will continue on their pre-switch antipsychotic medication while being tapered off any prohibited medications (Section 10.3.2) in a manner that is consistent with labeling recommendations and conventional medical practices. Non-prohibited psychotropic medications other than the pre-switch antipsychotic may be continued during the study but must have been stable for at least 6 weeks prior to Screening and should be maintained at a stable dose and regimen (see Section 10.3.1).

Subjects who are being treated with two antipsychotic medications will be permitted to enter the Screening Period. At the start of Screening, the Investigator will determine which antipsychotic medication is considered "primary", and the other one will be tapered off during the Screening Period.

Subjects who screen fail may be re-screened twice, 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.

Open-label Treatment Period (8 weeks):

At Baseline (Day 1) (pre-switch [PS] Baseline), subjects who have successfully completed Screening and have met the eligibility criteria will begin open-label treatment with SEP-363856 while continuing to take the full dose of their pre-switch antipsychotic. SEP-363856 dosing will begin the evening of the PS Baseline visit and 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 evaluated at PS Baseline and weekly throughout the rest of the study. Section 10.3 describes the circumstances and specifications for which prior and concomitant psychotropic medications other than the pre-switch antipsychotic are allowed in this study.

Subjects will receive SEP-363856 50 mg/day from Day 1 through Day 3 and 75 mg/day from Day 4 through Day 7. Every effort should be made to maintain subjects at 75 mg/day from Day 4 through Day 7. Beginning on Day 8, the dose of SEP-363856 can be adjusted in increments of 25 mg among 3 dose levels (50, 75 and 100 mg), according to the following requirements:

- The SEP--363856 dose should be increased to 100 mg/day on Day 8 to help ensure adequate coverage of symptoms, provided there are no significant tolerability problems as judged by the Investigator. Dose increases are to be made no more frequently than weekly to the next highest dose level (in 25 mg increments). Increases in dose will occur at regularly scheduled study visits, when possible. Dose increases between regularly scheduled visits may occur after prospective approval by the Medical Monitor. 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.
- SEP-363856 dose reductions can be made to the next lowest dose level (in 25 mg increments) at any time beginning on Day 8 for safety and intolerability issues as

judged by the Investigator. If a dose decrease is needed between study visits, subjects will be asked to return to the clinic for an unscheduled visit for drug dispensation.

Beginning on Day 8, the Investigator is permitted to start tapering the subject's pre-switch antipsychotic (further guidelines are provided in Section 21 Appendix II). The Investigator has the discretion to complete the discontinuation of the pre-switch antipsychotic by the end of Weeks 2, 3, 4, 5, or 6. As outlined in Section 10.3.4, concomitant medications for the treatment of extrapyramidal symptoms (EPS) and akathisia will be tapered during the antipsychotic tapering period. Once the pre-switch antipsychotic has been fully discontinued, subjects will remain on SEP-363856 (50 to 100 mg/day) until the end of Week 8.

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

Subjects who complete the 8-week Open-label Treatment Period will be eligible to participate in a separate open-label extension study (Study SEP361-309). Subjects who early terminate (ET) from the SEP361-308 study are not eligible to enroll in SEP361-309.

Follow-up Period (1 week):

Subjects who take any dose of SEP-363856 then discontinue early from the study or complete study and do not enter the extension study (Study SEP361-309) 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 an open label, flexibly dosed SEP-363856 (50 to 100 mg/day) study.

7.2.2. Blinding

This is an open label study.

7.2.3. Emergency Unblinding Procedures

This is an open label study.

7.3. Rationale

7.3.1. Rationale for the Study Design

The 8-week, outpatient, single-group, open-label design with flexible dosing and flexible switch duration was chosen to approximate a usual care setting for stable outpatients with schizophrenia who are in need of a switch from a previous antipsychotic. There will be a screening period to confirm diagnosis and ensure enrollment criteria are met. Subjects who satisfy enrollment criteria will be maintained on an antipsychotic treatment and enter an 8-week switch period where SEP-363856 is introduced during the first week using the same procedure as has been used in prior phase 2 and phase 3 studies (ie, start at 50 mg/day for Days 1-3, followed by 75 mg/day for Days 4-7). The pre-switch antipsychotic will not be adjusted during the first week of the study while Investigators are introducing SEP-363856. Beginning on Day 8, Investigators

will have the option to taper the pre-switch antipsychotic by the end of Week 2, 3, 4, 5, or 6. The variable duration for tapering of the pre-switch antipsychotic is intended to approximate a real-world clinical environment whereby the Investigator considers the needs of the individual patient as well as clinically relevant issues that could influence the switch outcome, such as reason for switch, type of pre-switch antipsychotic, dosage etc. Concomitant psychotropic medications that serve as adjuncts to antipsychotic treatment are common in clinical management of schizophrenia, and the study design permits enrollment of subjects taking non-prohibited concomitant psychotropic medications to support generalizability of the study results (see Section 10.3.1). All study subjects who complete the 8-week switch period will have experienced a minimum of 2 weeks on SEP-363856 monotherapy.

Study completers will be eligible to roll over into the 24-week open label extension study SEP361-309 for purposes of evaluating longer-term safety and tolerability as well as effectiveness of SEP-363856 in subjects switched from typical or atypical antipsychotic agents.

7.3.2. Rationale for the Dosages

Selection of these doses was guided by the results from 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 Study SEP361-201, which demonstrated a statistically significant difference in change from Baseline to Week 4 in PANSS total score for SEP-363856 (50 to 75 mg/day flexible dose) versus placebo in adults with an acute exacerbation of schizophrenia and which showed that SEP-363856 at doses of 50 to 75 mg/day for up to 28 days was well-tolerated.

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 adult subjects with schizophrenia was determined as 75 mg/day. The only 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. The dose of 100 mg/day was chosen because it is the highest dose in the proposed therapeutic dose range being examined in the ongoing Phase 3 program (25 to 100 mg).

7.3.3. Rationale for the Study Population

The study population will be similar to the population studied in other clinical switch studies in this indication. It will be comprised of adult outpatients aged 18 to 65 years old with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders – Fifth

Edition (DSM-5). Due to the outpatient nature of this study, subjects are also required to be judged psychiatrically stable, having had no evidence of an acute exacerbation of schizophrenia for at least 8 weeks prior to Baseline, no hospitalizations for psychiatric illness for at least 8 weeks prior to screening, and are taking a stable antipsychotic regimen for at least 6 weeks prior to screening. Subjects must be judged by the Investigator to be an appropriate candidate for switching current antipsychotic medication due to safety or tolerability concerns and/or insufficient efficacy. Subjects who are taking additional psychotropic medications are being permitted in the study in order to enroll subjects who are representative of the target schizophrenia clinical population in support of sample generalizability to the schizophrenia population at large.

7.3.4. Rationale for the Endpoints

The objective of this study is to demonstrate that clinically stable outpatients with schizophrenia who are in need of a switch from their current antipsychotic treatment can be safely and effectively transitioned to SEP-363856. The primary outcome measure, discontinuations due to clinical reasons, is a descriptive measure providing a percentage of subjects who drop out of the study due to safety or lack of efficacy. The secondary outcome measure, discontinuations due to any reason, is a similar descriptive index producing a percentage of subjects who drop out of the study for all causes, including but not limited to clinical reasons. Together, these endpoints will provide important information on the likelihood of a successful switch from a previous antipsychotic treatment to SEP-363856. Other endpoints in this study include standard safety measures (eg, AE's, SAE's, movement disorder measures, cardiometabolic measures) and validated efficacy assessments for schizophrenia (eg, PANSS, CGI-S, CGI-I) that were also employed in phase 2 and phase 3 studies of SEP-363856 for the purpose of providing important safety and efficacy data. Additionally, validated functional measures assessing social performance, medication satisfaction, quality of life, sleep, and healthcare utilization are intended to provide information on real-world and overall health aspects associated with transitioning between treatments.

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:

- Study is conducted as outpatient.
- Some concomitant psychotropic medications are allowed, as needed, during study participation.
- Dose reductions of SEP-363856 are allowed for drug tolerability purposes.
- Study centers are chosen based on a strong record of enrolling and retaining eligible subjects and producing quality data.
- 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.
- Data collection is monitored at the site level for adherence during the study.

See Section 15.3.10 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 (using the DSM-5 as a reference and confirmed using the Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID-5-CT]). The time since the subject's diagnosis must be ≥ 1 year prior to Screening. Every attempt should be made to obtain medical records or to have correspondence with a previous or current treating provider for the purposes of confirming that the previous course and treatment is consistent with schizophrenia.
6. Subject must have a CGI-S score ≤ 4 at Screening and Baseline.
7. Subject must have a PANSS total score ≤ 80 at Screening and Baseline.
8. Subject is judged to be clinically stable (ie, no evidence of an acute exacerbation of schizophrenia) by the Investigator for at least 8 weeks prior to Baseline.
9. Subject must not have been hospitalized for psychiatric illness for at least 8 weeks prior to Screening.
10. Subject must be judged by the Investigator to be an appropriate candidate for switching current antipsychotic medication due to safety or tolerability concerns and/or insufficient efficacy.
11. Subject is taking an oral antipsychotic and the antipsychotic regimen has been stable for at least 6 weeks prior to Screening. Subjects are permitted to remain on non-prohibited psychotropic medications other than the primary pre-switch antipsychotic that have been part of their ongoing treatment regimen as described in Section 10.3.1.
12. Subjects taking two antipsychotic medications (but not more) at screening are eligible for study inclusion, provided the total daily dose is equivalent to ≤ 12 mg/day haloperidol. However, the antipsychotic medication determined to be "secondary", based on Investigator judgment, must be discontinued prior to receiving SEP-363856. All subjects must be on a single antipsychotic medication at study baseline (Day 1).
13. Subject's body mass index (BMI) must be 18 kg/m2 to 40 kg/m2 (inclusive) at Screening.

14. For subjects taking nonpsychotropic medications for treating allowed chronic medical conditions, the dose and regimen must have been stable (± 25% total daily dose) for at least 30 days prior to screening.
15. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening.
16. Female subjects of childbearing potential must agree to use acceptable 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 requirement are provided in Section 10.4.
17. Male subjects must agree to avoid fathering a child and to use acceptable effective methods of birth control from screening until at least 30 days after the last study drug administration. Details on contraception requirement are provided in Section 10.4.
18. Subject is, in the opinion of the Investigator, generally healthy based on screening medical history, physical examination (PE), neurological examination, vital signs, electrocardiogram (ECG) and clinical laboratory values (hematology, chemistry and urinalysis).
19. Subject has a stable living arrangement at the time of Screening and anticipates stable living arrangement for the duration of the study.
20. Subject's eligibility confirmed through formal review process (See Section 10.6).

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

Note: For clinical laboratory criteria, retesting is allowed once, and the retest results will be used to determine eligibility.

1. Subject has a current DSM-5 diagnosis or presence of symptoms consistent with a major psychiatric disorder, other than schizophrenia, that is the primary focus of treatment. Exclusionary disorders include but are not limited to alcohol use disorder within past 12 months, substance (other than nicotine or caffeine) use disorder within past 12 months), or lifetime history of schizoaffective disorder or bipolar I or II disorder.
2. 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.
3. Subject is receiving a total daily dose of antipsychotic medication equivalent to > 12 mg/day haloperidol at Screening (See Section 22, Appendix III for haloperidol equivalent doses for common oral antipsychotic medications).
4. Subject has demonstrated a clinically significant change in symptom status according to Investigator judgment between Screening and Baseline.
5. 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 (ie, in the past one month) or at Baseline (ie, since last visit).

6. Subject is at significant risk of harming self or others based on Investigator's judgment.
7. Subject has attempted suicide within 6 months prior to Screening.
8. Subject has received treatment with any of the following psychotropic medications, which are prohibited during the study, unless the following washout requirements are met (See Section 10.3.2 for further details):
   - Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to receiving SEP-363856.
   - 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. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued prior to Study Day 1 dosing over a 1–2-week period, as judged to be safe by the Investigator.
   - Depot neuroleptics must have been discontinued at least 6 weeks or one cycle (whichever is longer) prior to receiving SEP-363856.
9. Subject has received electroconvulsive therapy (ECT) treatment within the 3 months prior to Screening or is expected to require ECT during the study.
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 (Note: Every attempt should be made to obtain medical records for any pre-existing medical conditions that impact a subject's eligibility):
    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 receiving SEP-363856 in the study.
    b. Subject has a history of neuroleptic malignant syndrome or serotonin 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. Subject has a history of malabsorption.
    f. 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. A repeat ECG for determination of eligibility may be administered once during the Screening Period and once at Baseline; requests for additional repeat ECGs must be discussed with the Medical Monitor. The repeat ECG during Screening can be conducted on a different day within the Screening Period, if needed.

g. Subjects with known history of human immunodeficiency virus (HIV) seropositivity.
h. Subject has type I diabetes mellitus or insulin-dependent type II diabetes.
i. In the Investigator's judgment, the subject has current symptoms suggestive of a diagnosis of Coronavirus Disease 2019 (COVID-19), or the presence of long-term medical, neurologic, or psychiatric sequelae of prior COVID-19.

11. Subject has a history of sick sinus syndrome, second or third-degree atrioventricular (AV) block, New York Heart Association (NYHA) Class II-IV heart failure, congenital long QT syndrome, or ECG findings of myocardial ischemia/infarction or the following cardiac arrhythmias: atrial flutter or fibrillation, junctional rhythm, idioventricular rhythm, supraventricular tachycardia, ventricular tachycardia.
12. Female subject who is pregnant or lactating.
13. Subject with a supine systolic blood pressure ≥ 150 mmHg and/or supine diastolic blood pressure ≥ 95 at Screening or Baseline. A repeat blood pressure measurement is allowed once during the Screening Period and once at Baseline; requests for additional repeat blood pressure measurements for determination of eligibility must be discussed with the Medical Monitor. The repeat blood pressure measurement at Screening can be conducted on a different day within the screening period, if needed.
14. Subject has any clinically significant abnormal laboratory value(s) at Screening (hematology, chemistry, and urinalysis) as determined by the Investigator. (Note: Retesting to determine eligibility is allowed once during the Screening Period. Abnormal findings of questionable significance will be discussed with the Medical Monitor prior to including any subject.)
15. 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.
16. Subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times the upper limit of the reference ranges provided by the central laboratory at Screening.
17. 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.
18. For subjects who do not have type 2 diabetes mellitus or glucose intolerance, screening glucose must be ≤ 125 mg/dL / 6.9 mmol/L (fasting) or ≤ 179 mg/dL / 9.9 mmol/L

(nonfasting). If nonfasting screening glucose is greater than this value, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL / 6.9 mmol/L. Hemoglobin A1c (HbA1c) must be ≤ 7%.

Subjects with type 2 diabetes mellitus or glucose intolerance are excluded unless their condition is stable as determined by satisfying ALL of the following:

a. Glucose must be ≤ 179 mg/dL / 9.9 mmol/L (fasting) or < 200 mg/dL / 11.1 mmol/L (nonfasting). If nonfasting screening glucose is ≥ 200 mg/dL / 11.1 mmol/L, subjects must be retested in a fasted state and the retest value must be ≤ 179 mg/dL / 9.9 mmol/L.
b. Hemoglobin A1c (HbA1c) must be < 8.0%, AND
c. Subject has been maintained on a stable regimen of oral or non-insulin injectable anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening.
d. Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND
e. Subject's diabetes is not newly diagnosed during screening for the trial.

19. 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 nonpsychotropic drug-related causes of elevated prolactin levels.
20. 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); note that this provision does not apply to prescribed cannabinoids, which are excluded.
21. Subject has received an investigational product or device within 90 days prior to signing informed consent. Subjects who have participated in COVID vaccine related studies will be permitted, provided they meet the 90-day criterion.
22. Subject has previously received SEP-363856.
23. Subject is a staff member of the study center or the relative of a staff member of the study center.
24. 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

Table 5: Investigational Product

Attribute	Investigational Product		
Product name	SEP-363856	SEP-363856	SEP-363856
Dosage form	Tablet	Tablet	Tablet
Dosage strength	50 mg	75 mg	100 mg
Route of administration	Oral	Oral	Oral
Physical description	Yellow oval tablet	Yellow oval tablet	Yellow oval tablet
Active Pharmaceutical ingredient (API)	SEP-363856-01 (hydrochloride salt)	SEP-363856-01 (hydrochloride salt)	SEP-363856-01 (hydrochloride salt)
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

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in one-week blister cards containing 9 tablets of SEP-363856 (7 days + 2 extra days).

9.2.2. Labeling Description

All packaging for the study medications will be labeled with:

- Protocol number
- Sponsor's name and address
- Name of investigational drug and dosage form
- Contents (eg, number of tablets)
- Investigational New Drug/caution statement

- Batch number
- Blank space to record visit number
- Blank space for subject identifiers
- Unique medication /kit ID number

9.3. Study Drug Storage

All study drug should be stored at 15°C to 25°C (59°F to 77°F). Excursions of 9°C to 30°C (48°F to 86°F) are permitted during shipment of study drug to investigational sites.

9.4. Dispensing of Study Drug

A Randomization and Trial Supply Management (RTSM) System (also referred to as Interactive web-based response system [IWRS]) will be used to manage subject screening and enrollment. The RTSM is an integrated web-based subject and drug management system.

Blister cards containing SEP-363856 tablets will be assigned by the RTSM based on the treatment schedule. The RTSM will generate instructions for which blister card (Medication No.) to dispense to each subject at each visit. RTSM drug dispensing guidelines should be followed for dispensing study drug to the subject. A specific user manual will be supplied.

Subjects will take one tablet of study drug per day at approximately the same time each evening at bedtime. Study drug may be taken without regard for food.

9.5. Study Drug Accountability

The Investigator or designee is responsible for maintaining adequate and up to date records of study drug disposition that includes the dates and quantity of dispensations, and use/return by subjects.

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

The RTSM will also be used for the accountability of the study drug at the clinical site. The Investigator or designee will maintain the records for accountability within RTSM, 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 the 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 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 will consist of SEP-363856 50 mg, 75 mg, or 100 mg tablets administered orally once daily and will be supplied as described in Section 9.

Subjects will take study drug at approximately the same time each evening at bedtime without regard for food.

10.1.1. Dose Adjustment Criteria for SEP-363856

Subjects will receive SEP-363856 50 mg/day from Day 1 through Day 3 and 75 mg/day from Day 4 through Day 7. Every effort should be made to maintain subjects at 75 mg/day from Day 4 through Day 7. Beginning on Day 8, the dose of SEP-363856 can be adjusted in increments of 25 mg among 3 dose levels (50, 75 and 100 mg), according to the following requirements:

> The SEP-363856 dose should be increased to 100 mg/day on Day 8 to help ensure adequate coverage of symptoms, provided there are no significant tolerability problems as judged by the Investigator. Dose increases are to be made no more frequently than weekly to the next highest dose level (in 25 mg increments). Increases in dose will occur at regularly scheduled study visits, when possible. Dose increases between regularly scheduled visits may occur after prospective approval by the Medical Monitor. 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 (see Section 11.9.12).

Beginning on Day 8, the SEP-363856 dose can be decreased at any time in 25 mg increments (including less than weekly intervals) as needed for safety or intolerability concerns as judged by the Investigator. If a dose decrease is needed between study visits, subjects will be asked to return to the clinic for an unscheduled visit for drug dispensation (see Section 11.9.12).

10.1.2. Pre-switch Antipsychotic Taper

The pre-switch antipsychotic is held stable for the first week. Beginning on Day 8, the Investigator can start to taper pre-switch antipsychotic and has discretion to complete the taper by end of Week 2, 3, 4, 5, or 6. See Section 21 Appendix II for guidelines for pre-switch antipsychotic taper.

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 tablets and dividing the actual number of doses taken (per tablet 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. Subjects who take less than 75% of scheduled doses or take more than 125% of the scheduled doses during their entire participation in the study will be considered noncompliant. Evidence of

noncompliance must be immediately reported to the Clinical Research Associate (CRA) and/or Medical Monitor.

10.3. Prior and Concomitant Medications

Details on all medications taken in the 60 days prior to Screening (including dosing changes) will be recorded in electronic data capture (EDC).

Every effort should be made to collect medical and/or pharmacy records for medications used in the past 60 days on the electronic case report form (eCRF). However, if medical records cannot be obtained, prior medications are to be reported based on subject or 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 eCRF: Medication name, dose, frequency, route, start date and time, stop date and time, and indication.

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

10.3.1. Prior Medications

Subjects will remain on their pre-switch antipsychotic and switch to SEP-363856 as described in Section 7.1. Subjects who enter Screening on two antipsychotic medications must washout of their secondary antipsychotic prior to Baseline (see Section 8.1 Inclusion criterion 12). Subjects are permitted to remain on non-prohibited psychotropic medications other than the primary pre-switch antipsychotic or secondary antipsychotic, that have been part of their ongoing treatment regimen. Except for medications listed in Section 10.3.4, the psychotropic medication must have been stable for at least 6 weeks prior to Screening and will be maintained at a stable dose and regimen throughout study participation. Investigator requests to adjust the dose or frequency of these psychotropic medications based on specific clinical circumstances will be evaluated on a case-by-case basis upon discussion with the Medical Monitor.

Treatment with sedative hypnotics is permitted during the Screening/Washout Period but should be tapered as clinically appropriate prior to receiving SEP-363856. This is to conform with and adequately prepare the subject for the protocol-specified limitations applicable to these agents.

Treatment with medications used to treat movement disorders must be discontinued as outlined in Section 10.3.4.

See Section 10.3.4 for allowed concomitant psychotropic medications.

10.3.2. Prohibited Medications

Treatment with the following medications are prohibited during the treatment phase of this study and must be discontinued as outlined below in a manner that is consistent with labeling recommendations and conventional medical practice.

- MAO inhibitors must be discontinued at least 28 days prior to receiving SEP-363856.

- 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. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued prior to Study Day 1 dosing over a 1–2-week period, as judged to be safe by the Investigator.
- Depot neuroleptics must have been discontinued at least 6 weeks or one cycle (whichever is longer) prior to receiving SEP-363856.

Initiation or adjustment of additional 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 is 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, pre-switch antipsychotic during taper, and the acceptable medications described below under Allowed Concomitant Psychotropic Medications in Section 10.3.4) 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) treatment within the 3 months prior to Screening nor during the Treatment Period up through the Follow-up Visit. Subjects who received ECT treatment during the Treatment Period will be discontinued from the study.

10.3.4. Allowed Concomitant Psychotropic Medications

See Section 10.3.1 for when subjects are permitted to remain on psychotropic medications other than the pre-switch antipsychotic during the study.

Treatment with benztropine up to 6 mg/day is permitted, as needed, for extrapyramidal symptoms (EPS). 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 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 EPS should not be given prophylactically. They are to be tapered and discontinued while the pre-switch antipsychotic is being tapered in a manner that is consistent with labeling recommendations and conventional medical practice. These medications may be reinstated, after consultation with the Medical Monitor, if EPS or akathisia symptoms emerge after treatment discontinuation.

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

- Oral lorazepam is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular (IM) lorazepam is permitted up to 4 mg/day for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per Investigator judgment.
- Temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, as needed.
- 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.
- 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 (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other).

Similar drugs at equivalent dosages may be permitted after consultation with the Medical Monitor.

The following requirements are not applicable to nonprohibited psychotropic medications that have been part of their ongoing treatment regimen. The date and time of the last dose of any concomitant psychotropic medication(s) taken prior to scheduled effectiveness 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 effectiveness 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.

10.3.5. Concomitant Non-psychotropic Medications

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after receiving SEP-363856 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 receiving SEP-363856 (or be discontinued). This includes β-adrenergic antagonists and other medications used to treat stable hypertension. Routine vaccines (ie, seasonal influenza, pneumonia, COVID-19, etc.) are allowed based on the Investigator's judgment.

In addition, use of non-prescription pain medications (eg, 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.

Female subjects may use contraception as detailed in Section 10.4.

10.4. 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.
  - Exclusively in a same sex relationship (if this is the subject's usual lifestyle choice). Subject must have been exclusively engaging in same sex relations for at least 60 days prior to administration of the first dose of study drug, throughout the Study and for a minimum of 30 days after completion or premature discontinuation from the study drug.
  - Use of acceptable effective methods of contraception during the Treatment Period and for 30 days after last dose of study drug. Acceptable 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 acceptable 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.

10.5. 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. 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.

10.6. Eligibility Review Process

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

Sites will complete a form for each subject in screening, which provides information that supports the subject's appropriateness for participation in the study. In addition, data from 12-lead ECGs, vital sign measurements, and clinical laboratory tests may also be reviewed. Each form must be approved by the Sponsor or designee prior to the subject being enrolled.

In addition, audio recordings of the Screening PANSS scale may be reviewed by the Sponsor's designee with clinical expertise in PANSS scale administration. The outcome of the PANSS audio recording review may be utilized by the Sponsor or designee to evaluate the subject's eligibility.

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, age, sex, ethnicity, race), prior and current medications, and medical and psychiatric history will be collected.

A medical and psychiatric history will be obtained by the Investigator or qualified designee as listed on the Form Food and Drug Administration (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).

Subjects will be checked for multiple study enrollment at screening by clinical site staff using available registries of subjects participating in clinical trials. Sites will be provided training.

11.2. Prior and Concomitant Medication Review

See Section 10.3 for a complete description of medications permitted during the study. Prior and concomitant medications taken in the past 60 days will be recorded at Visit 1 (Screening). Thereafter, any changes in concomitant medications or new medications added up to Week 9 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-5-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 with at least 2 years of clinical experience with schizophrenia patients. The administration time is approximately 30 - 40 minutes.

11.4. 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 Screening or subsequently during study conduct.

11.4.1. 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.

11.4.2. Clinical Laboratory Tests

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

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) (or equivalent) certified.

Point of care rapid testing will be used for the rapid urine pregnancy test and rapid urine drug test.

Clinically significant laboratory assessment at Screening will be captured in the medical history in the CRF. Any clinically significant changes from Screening, as determined by the Investigator, will be noted as AEs in the CRF. Positive drug screen findings observed during study participation must be discussed with the Medical Monitor to assess and determine subject disposition.

11.4.3. 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 source and 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 will be obtained prior to clinical laboratory collection.

Clinically significant vital sign abnormalities at Screening will be captured in the medical history in the CRF. Any clinically significant changes from Screening, as determined by the Investigator, will be noted as AEs in the CRF.

11.4.4. 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. Refer to Section 20, Appendix I for additional information. ECG parameters to be collected include ventricular heart rate (beats/min), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec), and 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 continuation 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 ECG changes from Screening, as determined by the Investigator, will be noted as AEs in the CRF.

ECGs with possibly drug-related or clinically significant abormal 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.

11.4.5. Physical and Neurological Examination

Complete PEs as well as neurological exams 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.

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

11.4.6. Safety Scales

Raters will receive specific training regarding each assessment prior to performing scales.

11.4.6.1. Simpson-Angus Scale (SAS)

The SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale of severity, and address rigidity, gait

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

11.4.6.2. Barnes Akathisia Rating Scale (BARS)

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

11.4.6.3. 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 will be administered by a qualified rater at the site.

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

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

If a 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 any post-Baseline C-SSRS assessment, an associated AE must be reported.

11.4.6.5. Pittsburgh Sleep Quality Index (PSQI)

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

11.5. Effectiveness Assessments

Raters will receive specific training regarding each assessment prior to performing assessments.

11.5.1. 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 subscales: the Positive subscale assesses hallucinations, delusions, and related symptoms; the Negative subscale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology subscale 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 subscales, 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 to 40 minutes (Kay-1994, Opler-1992; Perkins-2000). The PANSS requires input from an informant (eg, caregiver, relative, friend, case worker, or hospital staff). PANSS interviews will be audio recorded and the recording may be reviewed by Sponsor's designee to monitor the quality of the rater interviews, where allowed by local/regional regulations. No identifying information will be associated with the audio recording. PANSS raters will be required to meet specific training and education criteria before they are certified to rate for this study.

11.5.2. 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.

11.5.3. Clinical Global Impressions – Improvement Scale (CGI-I)

The CGI-I scale is a standard 7-point scale (Guy-1976) that requires the clinician to assess how much the subject's overall symptoms have improved or worsened relative to a baseline state. The CGI-I will be administered by a qualified rater at the site.

11.5.4. 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.

11.5.5. 12-Item Short Form Survey (SF-12)

The SF-12 is a 12-item self-reported questionnaire that is a subset of the SF-36 Health Survey. The survey captures physical and mental health. There are 8 subscales including: Physical functioning, Role-physical, Bodily pain, General health, Vitality, Social Functioning, Role emotional, and Mental health. The responses are reported on a 3- or 5-point Likert scale, depending on the question. The SF-12 uses 2-items each to estimate scores for 4 of the 8 health concepts (physical functioning, role-physical, role-emotional, and mental health). Score for the remaining 4 healthy concepts (bodily pain, general health, vitality, and social functioning) are estimated using 1 item each. Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12) are computed using the scores of 12 questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. The SF-12 will be administered by a qualified rater at the site.

11.5.6. Personal and Social Performance Scale (PSP)

The PSP is a 100-point single-item rating scale of personal and social functioning (Morosini-2000). The rating is based on the assessment of a patient's functioning in four areas: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Higher scores indicate better functioning. Scores of 0-30 indicate poor functioning; scores of 31-70 indicate varying degrees of difficulty; and scores of 71-100 reflect only mild difficulties at most. The PSP will be administered by a qualified rater at the site.

11.5.7. Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, patient-rated questionnaire that requires the subject to use a 7-point, Likert-type scale to rate how satisfied they are with their current antipsychotic medication (antipsychotic medication taken at the time of screening or within 30 days of screening) (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

11.5.8. Healthcare Resource Utilization

Healthcare resource utilization will be assessed by recording the following at Baseline:

- 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)

Healthcare resource utilization will be assessed by recording the following post Baseline:

- Number of physician office visits, emergency room visits, and hospitalizations (total number and number related to schizophrenia) since prior assessment
- Length of each hospital stay since prior assessment
- Employment status since prior assessment
- The average number of hours a caregiver(s) spends helping the subject per week (since prior assessment)

11.5.9. Nicotine Use Information

Information regarding the subject's nicotine use will be recorded in the eCRF. Data collected will include the type of nicotine used, approximate amount and time period during which nicotine was / is being used.

11.6. Pharmacokinetic Assessments

All blood samples for determination of plasma SEP-363856 concentrations will be obtained at the same time that other blood samples are taken whenever possible. Date and time of sample collection as well as date and time of the previous dose of study drug prior to pharmacokinetic (PK) blood sampling and the date and clock time of blood sampling, must be recorded. Plasma SEP-363856 concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Population pharmacokinetics (POPPK) analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SEP-363856 exposure will be explored using population PK/pharmacodynamics (PD) methods and reported separately. See Section 24, Appendix V for details including instructions of processing blood samples for plasma.

Plasma samples collected for PK concentration analysis CCI

CCI

11.8. Tokenization

The participant will be asked for optional consent to allow access to their medical data.

To allow the linking of subject participants records from different sources, ie, data collected as part of the study as specified in this Protocol and longitudinal real-world data such as electronic health record, claims, and laboratory data from other care settings, without compromising the participant's confidentiality, tokenization and matching procedures will be utilized for US participants only. The tokenization process starts with each data provider generating a token behind the firewall via proprietary software. Personal information such as names and dates of birth from study participants are removed from real-world data sources and replaced with encrypted, one-way, hashed identifiers, and then further encrypted using asymmetric keys in compliance with Health Insurance Portability and Accountability Act (HIPAA). This encrypted information is sent for matching to the anonymized participant master index. While it is not possible to reverse the hash, source-specific tokens can be decrypted and re-encrypted so that records can be linked across sources. The result of the process is a unique anonymized identifier for each participant, which can be used to link participant records across sources (real world data and study data).

Information from the tokenization procedure will not be reported in the clinical study report.

11.9. Study Visits and Assessments

See Table 2, for a summary of procedures at each study visit. See Section 11.1 to Section 11.7 for detailed information on conducting assessments.

It is suggested that rating scales be completed in the following sequence, if possible. If the sequence must be changed, it is strongly suggested to complete the CGI-S and CGI-I scales after the other clinician-rated scales. The Investigator is encouraged to maintain the same sequence across visits for individual subjects.

Screening Visit (V1)	**Baseline (V2) to Visit 10 (V10)** Assessments will be collected at each visit as specified in Table 2	**Visit 11 (V11) (Week 9 / Follow-up)**
1. SCID-5-CT	1. PANSS	1.C-SSRS
2. PANSS	2. BNSS	
3. C-SSRS	3. C-SSRS	
4. CGI-S	4. SAS/BARS/AIMS	
	5. PSP	
	6. Healthcare resource utilization (HRU)	
	7. CGI-S	
	8. CGI-I	
	9. PSQI	
	10. SF-12	
	11. MSQ	

Note: Rating assessments will be performed by the rater or subject using an electronic tablet. In the event that the electronic tablet is not available or assessment not available on the tablet, the rating assessments will be performed by the rater or subject using a paper version of the assessment. SCID-5-CT will be performed using a paper version.

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

After a subject provides consent, a unique subject number will be assigned at screening by the RTSM system, 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 #006 will be 308006002). 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 and the open-label extension (OLE) study.

Subjects will be evaluated at the Screening Visit to determine their eligibility for the study. Screening assessments may occur over multiple days. The subject's eligibility assessment will be reviewed by the sponsor and/or designee based on protocol specified inclusion and exclusion criteria. In the event the sponsor/designee 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 up on leaving the study.

Subjects who screen fail may be re-screened up to two times, 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
- Obtain informed consent for duplicate subject check

CCI [redacted]

- Review inclusion and exclusion criteria
- Collect prior and concomitant medications
- Obtain demographic information
- Collect medical history
- Collect psychiatric history
- Collect nicotine use information
- SCID-5CT
- Physical and neurological examination including height and weight; clinical site staff to calculate and record BMI
- Vital sign measurements
- 12-lead ECG
- Blood samples for clinical laboratory evaluation (hematology and serum chemistry). If possible, subjects should fast for at least 8 hours prior to avoid potential for retest.
- Blood samples for serum pregnancy test (serum human chorionic gonadotropin [βhCG]) for female subjects 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
- CGI-S
- C-SSRS
- Collect adverse events (Note: events occurring prior to first dose of study drug will be identified programmatically as pretreatment events.)
- Duplicate subject check (where local regulations allow)
- Obtain signed consent for optional Tokenization
- Obtain confirmation of subject's eligibility through formal review process (Inclusion Criterion 20).

11.9.2. Pre-switch (PS) Baseline: Visit 2 (Day 1) – Treatment Period

The following procedures will be conducted during this visit:

CCI

- Review inclusion and exclusion criteria
- Collect concomitant medications
- Vital sign measurements
- Weight and waist circumference (BMI derived in the electronic data system)
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)
- Blood sample for POPPK

CCI

- Urine sample for urinalysis, UDS, and βhCG (for female subjects)
- PANSS
- CGI-S
- BNSS
- PSQI
- C-SSRS
- SAS
- BARS
- AIMS
- SF-12
- MSQ
- PSP
- HCRU (last 3-month lookback)
- Collect adverse events (Note: events occurring prior to first dose [on Day 1] of study drug will be identified programmatically as pretreatment events.)
- Dispense study drug

11.9.3. Visit 3 (Week 1; Day 8 + 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- Blood sample POPPK
- PANSS
- CGI-S
- CGI-I
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.9.4. Visit 4 (Week 2; Day 15 ± 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- PANSS
- CGI-S
- CGI-I
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.9.5. Visit 5 (Week 3; Day 22 ± 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.9.6. Visit 6 (Week 4; Day 29 ± 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- Weight and waist circumference (BMI derived in the electronic data system)
- Blood sample for POPPK
- Urine sample for βhCG (for female subjects) and UDS
- PANSS
- CGI-S
- CGI-I
- BNSS
- PSQI
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.9.7. Visit 7 (Week 5; Day 36 ± 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.9.8. Visit 8 (Week 6; Day 43 ± 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- PANSS
- CGI-S
- CGI-I
- C-SSRS
- Collect adverse events

- Study drug accountability
- Dispense study drug

11.9.9. Visit 9 Telephone Contact (Week 7; Day 50 ± 2 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- C-SSRS
- Collect adverse events

11.9.10. Visit 10, End of Treatment (EOT) or Early Termination (ET) - (Week 8; Day 57 ± 2 days)

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Collect nicotine use information
- Physical and neurological examination
- Vital sign measurements
- Weight and waist circumference (BMI derived in the electronic data system)
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry) and β-hCG (for female subjects)
- Blood sample for POPPK
- Urine sample for urinalysis, rapid urine β-hCG (females), rapid urine drug screen, and UDS
- PANSS
- CGI-S
- CGI-I
- BNSS
- PSQI
- C-SSRS
- SAS
- BARS
- AIMS
- SF-12
- MSQ

- PSP
- HCRU (since last visit)
- Collect adverse events
- Study drug accountability
- Duplicate subject check

At this visit, subjects who have participated throughout the duration of the Treatment Period, up to and including Week 8 will have the option to enroll and continue treatment in an open -label extension study (Study SEP361-309).

For subjects entering the extension study, the Week 8 Visit in this study (SEP361-308) will serve as the OLE Baseline visit for the extension study (SEP361-309) and subjects will not need to return for further visits in this study.

Subjects who do not enter the extension study will complete the Follow-up Period.

11.9.11. Visit 11 (7 ± 2 days after last dose) - Follow-up Period

All subjects who discontinue early or do not elect to enroll in the open-label extension study (Study SEP361-309) 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, administration of C-SSRS, and collection of AEs and concomitant medications may occur by telephone contact if the subject is unable to come to the clinic for the Follow-up Visit.

The following procedures will be conducted during this visit:

- Concomitant medications
- Physical and neurological examinations
- Vital sign measurements
- Urine sample for βhCG (for female subjects)
- C-SSRS
- Adverse events

11.9.12. 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
- Adverse event 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 (including Follow-up Visit for those not enrolling in open-label extension).

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.

If a 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 any post-Baseline C-SSRS assessment, an associated AE must be reported.

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

Any clinically significant changes from Screening in objective findings (eg, clinical laboratory value, ECG value, vital sign values and physical / neurological examination observation), as determined by the Investigator, will 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. 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 or clinical significance 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 pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. Pre-treatment events and AEs and SAEs that occur from the signing of informed consent to the subject's last study visit must be recorded on the CRF. Determination of whether an event is a pre-treatment event, or an adverse event will be made programmatically by the Sponsor or designee, not by the site.

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. Additional information will be collected for the non-serious psychiatric AEs that led to discontinuation from the study as well as all serious psychiatric AEs within the study. 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 those 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-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 not more than 24 hours after the Investigator or study center staff become aware of the event. Response to specific questions included on the SAE form for psychiatric SAEs is required. 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 an 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 medication 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 medication. 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 medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth). Infants may be followed for up to one year following 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 the 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.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

13. TERMINATION OF SUBJECT FROM STUDY

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)
- 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 discontinuation of "Lack of efficacy" should be selected when a subject early terminates from the study because there has been insufficient therapeutic benefit of the study drug (perceived or actual) and the subject's baseline condition has neither worsened nor improved significantly.

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 who prematurely discontinue from the study treatment (ie, do not complete through Week 8), every effort should be made to complete the final evaluation procedures, in accordance with the ET visit described in Section 11.9.10.

Subjects who complete the study but do not elect to enroll in the open-label extension study (Study SEP361-309) and those subjects who discontinue the study early will complete a follow up visit 7 (±2) days after the last dose of study drug as described in Section 11.9.11.

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 medication 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 undergo final evaluation procedures in accordance with the early termination (ET) visit described in Section 11.9.10 and safety Follow-up Visit as described in Section 11.9.11.

15. STATISTICS

The Statistical Analysis Plan (SAP) will provide the details on the statistical methods planned for this study and will be finalized before the database lock of the study.

15.1. Sample Size

Approximately 120 subjects will be required for this study. This sample size was determined by the width of the 95% confidence interval for the proportion of subjects who may discontinue due to clinical reasons by Week 8 to ensure the precision of the estimate of the true discontinuation rate due to clinical reasons. Assuming, 1) 15% of SEP-363856 treated subjects will experience discontinuation due to clinical reasons by Week 8, and 2) 6.4% as the half width (the distance between the upper/lower limits to the point estimate) of the 95% confidence interval (ie, [8.6%, 21.4%]), approximately 120 subjects will be required.

15.2. Analysis Populations

15.2.1. Safety Population

The safety population will consist of all subjects who are enrolled and receive study medication. All safety and tolerability assessments will be performed using the safety population.

15.2.2. Effectiveness Population

The effectiveness population will consist of all subjects who are enrolled, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline effectiveness measurement in PANSS or CGI-S. Subjects will be included in the population regardless of any protocol deviation. The effectiveness population will be the primary population for the effectiveness analyses.

15.3. Data Analysis

Descriptive statistics will be compiled for all endpoints.

15.3.1. Subject Disposition

Subject disposition will be summarized for all subjects. The number and percentage of subjects, who are screened, screen-failed, enrolled, received study drug, and completed or discontinued early from the open-label treatment period will be presented.

15.3.2. Study Drug Exposure and Compliance

Descriptive statistics on treatment exposure and treatment compliance will be summarized for the safety population.

Exposure, defined as number and percentage of subjects with ≥ 1, ≥ 7, ≥ 14, ≥ 21, ≥ 28, ≥ 35, ≥ 42, ≥ 49, and ≥ 56 days exposure, will be compiled. Descriptive statistics (n, mean, standard deviation, median, 25^{th} and 75^{th} percentile, minimum, and maximum) will also be calculated on exposure in days. Duration of exposure (in days) will be calculated as: last dose date - first study dose date + 1. An additional listing will also be generated to display the length of time that each subject received pre-switch anti-psychotic medication (with corresponding name and dosage).

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 (ie. 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 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 reviews of data listings and the protocol deviations log. The IPD categories may include, but may not be limited to:

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

IPDs will be identified for all enrolled 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 (eg, age, gender, race, ethnicity, etc.) will be summarized for all screened subjects. In addition, demographic and baseline characteristics will be summarized for each defined analysis population. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized 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). Psychiatric history data will also be summarized for the safety population.

15.3.5. Safety Analyses

The primary analyses for this study will be performed for the safety endpoints, which are stated in Section 6.

15.3.5.1. Primary and Secondary Endpoint Analysis

The primary endpoint is the percentage of subjects who discontinued for clinical reasons, such as due to AE or lack of efficacy. This percentage will be calculated by a proportion consisting of the number of subjects who experience a discontinuation event due to clinical reasons as the numerator divided by the number of subjects in the safety population as the denominator multiplied by 100 along with a corresponding 95% confidence interval (CI).

The secondary endpoint is the percentage of subjects who discontinued for any reason (ie, all cause discontinuation). The percentage will be calculated similarly as that of the primary endpoint along with a corresponding 95% CI.

The number and percentage of subjects, who discontinued early from the open-label treatment period (including both clinical reasons, ie, discontinued due to an AE (primary endpoint) and any reason for discontinuation (secondary endpoint)) will be presented.

As an exploratory analysis, the time-to-discontinuation for both clinical reason and for any reason will be summarized descriptively, (eg, n, median, 25th percentile, 75th percentile, minimum and maximum, and 95% CI on median, where possible) and presented with corresponding Kaplan-Meier plots.

15.3.5.2. Adverse Events

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

The following summaries will be provided 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 will also be provided. In addition, summaries of all AEs, SAEs, and AEs leading to discontinuation by modal daily dose will be provided. 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 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.

15.3.5.3. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables and by-visit summaries of the observed values including the Week 8 last observation carried formula (LOCF) Endpoint along with change from Baseline values. 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.

15.3.5.4. ECGs

ECG analysis will be based on the centrally read data. Observed values and changes from Baseline in ECG parameters will be summarized along with shift in ECG overall assessment. 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. Fridericia's correction (QTcF) and Bazett's correction (QTcB) will be used for QT interval correction.

15.3.5.5. Vital Signs

Vital sign parameters will be summarized by presenting by visit and Week 8 LOCF endpoint summaries of the observed values and the change from Baseline values. 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.

15.3.5.6. 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.

15.3.5.7. Concomitant Medications

All medications will be coded to indication-specific Anatomical Therapeutic Chemical (ATC) classification (ie, 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 and by the drug class and preferred name for the safety population.

15.3.5.8. Suicidality Measure

Frequency and severity of suicidal ideation and suicidal behavior as measured by the C-SSRS scale will be summarized for the overall post-Baseline period and by visit.

15.3.5.9. Measures of Motor Function

Measures of motor function include SAS, BARS and AIMS. Descriptive statistics for these measures of motor function will be compiled for observed values and change-from-baseline by visit and for Week 8 LOCF endpoint. Additional analyses on the measures of motor function, as necessary, will be described in the SAP.

15.3.5.10. Pittsburgh Sleep Quality Index

Descriptive statistics for Pittsburgh Sleep Quality Index will be compiled for observed values and change from baseline by visit and for Week 8 LOCF endpoint.

15.3.5.11. Subgroup Analysis (Safety Parameters)

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

15.3.6. Effectiveness Analyses

SEP-363856 effectiveness will be evaluated by descriptive statistics on the following:

- Change from baseline in the PANSS total score and subscale scores (positive, negative, and general psychopathology) at Week 8
- Change from baseline in the PANSS Marder Factor (five-factor) score at Week 8
- Change from baseline in the CGI-S at Week 8
- Change from baseline in the BNSS at Week 8
- Change from baseline in the SF-12 at Week 8
- Change from baseline in the PSP at Week 8
- Change from baseline in the MSQ at Week 8
- CGI-I at Week 8

This is an uncontrolled, open-label study. Hence, no inferential statistics on efficacy / effectiveness will be presented. Descriptive statistics (ie, sample size, mean, standard deviation, minimum, median, maximum, and a 95% confidence interval) will be displayed for each visit, including the last visit and the Week 8 last-observation-carried-forward (LOCF) endpoint. The response variables will include the change from the baseline assessment (except CGI-I) and the endpoint assessments throughout the study. Confidence intervals will be based on means and standard deviations estimated without adjustment for any center or baseline effects.

15.3.6.1. Healthcare Resource Utilization

The number of physician's office visits, ER visits, and hospitalizations (for any reason and those related to schizophrenia) per month at Baseline and at Week 8, as well as the average length of hospital stays (for any reason and those related to schizophrenia), will be summarized. The frequency and percentage of subjects receiving unpaid care at each time point, along with the average number of hours a caregiver spends per week helping the subject, will also be summarized.

The change in the number of physician's office visits, ER visits, and hospitalizations, the average length of hospital stays, and the average number of hours a caregiver spends per week helping the subject from Baseline at Week 8 will be summarized. Shifts from Baseline to Week 8 in whether the subjects receive unpaid care will also be summarized.

15.3.6.2. Nicotine Use Information

Nicotine use data will be summarized descriptively at Baseline and Week 8 (end of treatment [EOT]/early termination [ET]). For each nicotine type, the amount being used at each visit in comparison with the amount being used at Baseline will be classified as "increased", "decreased", or "unchanged" for every subject, based on the reported amount used in a given period.

- Then for subjects whose changes in amount for all nicotine types between Baseline and Week 8 (end of treatment [EOT]/early termination [ET]) are not in opposite directions, a subject's overall nicotine consumption at each scheduled post-Baseline visit in comparison with Baseline will be classified as "increased", "decreased", or "unchanged".

The number and percentage of subjects in each overall consumption amount change category will be summarized.

In addition, for subjects who reported using "Cigarettes" at either Baseline or each scheduled post-Baseline visit or at both time points, the amount of cigarette used per day and the change from Baseline values will be summarized by visit.

Further details regarding the specifics of this analysis will be described in the SAP.

15.3.6.3. Adjustment for Multiplicity

Not applicable as only descriptive statistics for effectiveness parameters will be compiled.

15.3.7. Pharmacokinetic Analysis

Plasma concentrations of SEP-363856 will be presented in a data listing. Population pharmacokinetic (POPPK) analysis will be performed using plasma concentrations of SEP-363856, the results of which will be reported separately.

15.3.8. Pharmacodynamic Analysis

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

15.3.9. Interim Analysis

None planned.

15.3.10. Treatment of Missing Data

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

Missing data at Week 8 will be imputed using the LOCF approach. The LOCF endpoint is defined as the last non-missing value at a scheduled or unscheduled visit post-baseline during the treatment period excluding the follow-up visit.

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, POPPK, PGX 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 Regulation (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 or Description
Informed consent	A
Review inclusion/exclusion criteria	A
Prior/concomitant medication review	A
Dispensation of study drug	F
Study drug accountability	A, F
Demography	A
Medical history	A
Psychiatric history	A
Nicotine use information	A
SCID-5-CT	none
Physical and neurological examination	A
Height	A
Vital signs	A
Weight (including BMI)	A
Waist circumference	A
12-lead Electrocardiogram (ECG)	B
Hematology, chemistry, and urinalysis	G
Blood sample for hepatitis	G
Serum follicle stimulating hormone (FSH)	G
Serum human chorionic gonadotropin (β-hCG), (females)	G

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

Protocol Step	Computerized System Type or Description
CCI [redacted]	
Blood sample for POPPK	C
Urine drug screen	G
Rapid urine drug screen	A
Urine β-hCG (females)	G
Rapid urine β-hCG (females)	A
Positive and Negative Syndrome Scale (PANSS)	D
Clinical Global Impression – Severity (CGI-S)	D
Clinical Global Impression – Improvement (CGI-I)	D
Brief Negative Symptom Scale (BNSS)	D
Pittsburgh Sleep Quality Index (PSQI)	D
Columbia Suicide Severity Rating Scale (C-SSRS)	D
Simpson-Angus Scale (SAS)	D
Barnes Akathisia Rating Scale (BARS)	D
Abnormal Involuntary Movement Scale (AIMS)	D
SF-12	D
Medication Satisfaction Questionnaire (MSQ)	D
Personal and Social Performance Scale (PSP)	D
Healthcare Resource Utilization (HCRU)	D
Pretreatment/Adverse events (AE) monitoring	A
Duplicate Subject Check	E
Tokenization consent (optional)	A
Tokenization, if consent signed	H

A = EDC (Medidata RAVE); B =ECG central vendor; C = LIMS/ American Standard Code for Information Interchange (ASCII); D = Signant Health; E = Verified Clinical Trials; F = Randomization and Trial Supply Management System (RTSM); G = Central Laboratory; H = Datavant.
Abbreviations: EDC = electronic data capture; LIMS = laboratory information management system; SCID-5-CT = Structured Clinical Interview for DSM-5, Clinical Trials Version.

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 be conducted using techniques such as central review, personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with International Conference on Harmonization (ICH) Good Clinical Practice (GCP). On-site review will be conducted to ensure source documents and other trial records are accurate and complete and, where applicable, consistent with CRF entries.

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 standard operating procedures (SOPs), protocol, ICH GCP and local regulations. The PI or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the Independent Ethics Committee (IEC). Should the PI 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, Institutional Review Board (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, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.6. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s) and 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).

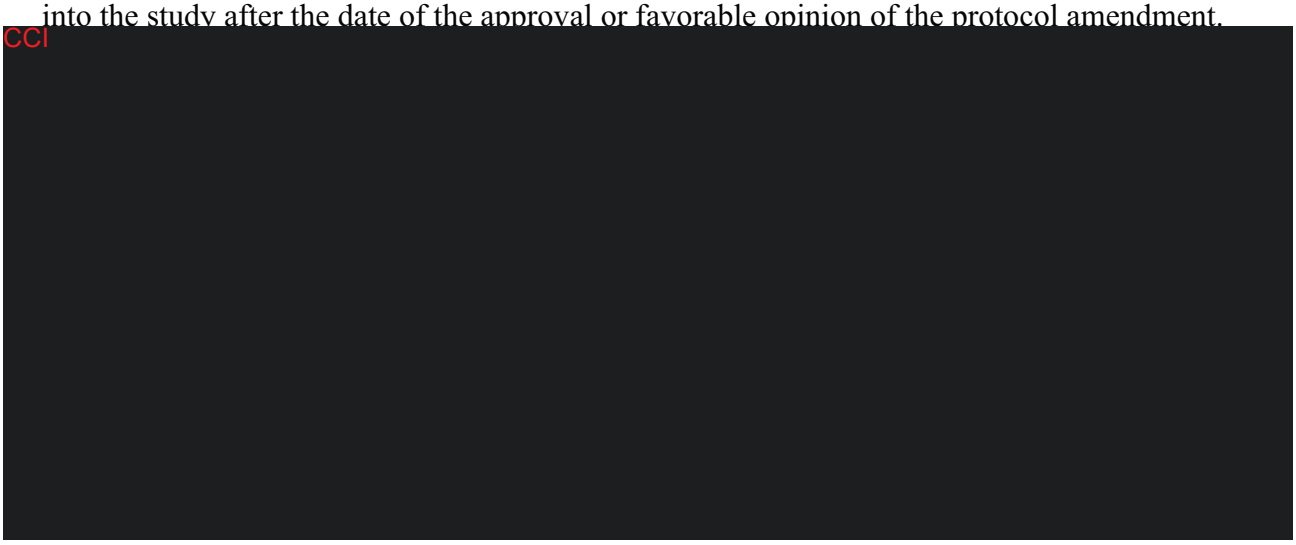
17.3. Informed Consent

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. 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. The Sponsor/CRO may submit informed consent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

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 medication, 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.

CCI



17.4. Subject Privacy

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

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

17.5. Protocol Amendments and Emergency Deviations

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

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately, 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 in the European Union [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 SEP361-308, Version 5.00 "An 8-Week, Open-Label Study Evaluating the Effectiveness, Safety and Tolerability of SEP-363856 in Subjects with Schizophrenia Switched from Typical or Atypical Antipsychotic Agents", 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 overread 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: GUIDELINE FOR PRE-SWITCH ANTIPSYCHOTIC TAPER

- Prior to the first dose of investigational product (IP), plan a taper strategy of the pre-switch antipsychotic for each subject (changes to the plan may be needed during the study based on subject response / tolerability)
    - Consider treatment history, clinical presentation and reason for switch
    - Attempt to reduce the pre-switch antipsychotic by at least 50% half-way through the taper
- If the pre-switch antipsychotic is considered to have a strong binding affinity for muscarinic-cholinergic (M1) and/or histaminergic (H1) receptors, consider a longer, more gradual taper (ie, 4 - 6 weeks to complete)
    - Examples: asenapine, olanzapine, quetiapine
- If the pre-switch antipsychotic is considered to have a strong binding affinity for dopaminergic (D2, D3) receptors, consider a moderately gradual taper (ie, 3 - 5 weeks to complete)
    - Examples: lurasidone, paliperidone, risperidone, ziprasidone, haloperidol (and other first-generation antipsychotics)
- If the pre-switch antipsychotic is considered to have a long half-life, a faster, less gradual taper may be appropriate (ie, 2 - 3 weeks to complete)
    - Examples: aripiprazole, brexpiprazole, cariprazine
- For any type of pre-switch antipsychotic, if the dose is at the upper end of the recommended daily dose range for that particular medication, consider a longer, more gradual taper
- If the subject has been taking a D2 antagonist for lengthy period of time, consider longer more gradual taper

22. APPENDIX III. HALOPERIDOL EQUIVALENT DOSES

Medications	Haloperidol Equivalent (12 mg)
Typical Antipsychotics	
Chlorpromazine	600 mg
Chlorprothixene	500 mg
Fluphenazine	15 mg
Haloperidol	12 mg
Perphenazine	40 mg
Thioridazine	500 mg
Thiothixene	30 mg
Trifluoperazine	25 mg

Medications	Haloperidol Equivalent (12 mg) in mg
Atypical Antipsychotics	
Amisulpride	800
Aripiprazole	30
Asenapine	30
Brexpiprazole	4.5
Cariprazine	4.5
Clozapine	900
Haloperidol	12
Iloperidone	24
Lurasidone	120
Olanzapine	20
Paliperidone	9
Quetiapine	700
Risperidone	6
Sertindole	36
Sulpiride	800
Ziprasidone	160

For antipsychotics not listed in the tables above, please consult the Medical Monitor.

References:

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23. APPENDIX IV. CLINICAL LABORATORY TESTS

Detailed instructions will be provided in a study center manual.

The following clinical laboratory tests are to be performed.

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)
Hemoglobin, Hematocrit, Platelet Count, 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), 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 / RAPID URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids (Urine Drug Screen), Cocaine, Marijuana (THC) (Rapid Urine Drug Screen), 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), Rapid 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.

24. APPENDIX V. PHARMACOKINETIC SAMPLING AND SAMPLE HANDLING GUIDELINE

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

BLOOD SAMPLES FOR PLASMA PHARMACOKINETICS

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

For each defined PK sampling time point, collect 6 mL blood sample into a K_2EDTA treated tube. Invert gently 8 to 10 times. Keep the blood collection tube on wet ice upon blood draw, and centrifuge for 20 minutes at ca. x 1300 g to isolate plasma within 30 minutes of blood draw. To ensure a more homogenous sample, all plasma samples should first be transferred to 1 tube, capped and mixed well. Split the harvest plasma sample into 2 polypropylene tubes with approximately equal volume, and label as Primary and Backup. Freeze plasma tubes in a freezer set at approximately -20°C or lower. The date and clock time of blood collection must be recorded.

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

All samples will be shipped with sufficient dry ice protection.

Study Day	Collection Time	Volume Collected
Day 1	Pre-dose	6 mL
Day 8	Anytime (Actual date and clock time will be recorded)	6 mL
Day 29	Anytime (Actual date and clock time will be recorded)	6 mL
Day 57 / EOT / ET	Anytime (Actual date and clock time will be recorded)	6 mL

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