SEP-363856
Clinical Study Protocol SEP361-309

An Open-label Extension Study to Assess the Safety and Tolerability of SEP-363856 in Subjects with Schizophrenia Switched from Typical or Atypical Antipsychotic Agents

IND No. 115,629

Version 3.00

28 March 2023

Incorporating Substantial Amendment 2.00

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	PPD , MD PPD PPD Psychiatry Sunovion Pharmaceuticals 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: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: SEP-363856

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

Title of Study: An Open-label Extension Study to Assess the 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 that have participated in Study SEP361-308

Phase of Development: 3

Study Objectives:

Primary:

- To evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (50, 75, 100 mg/day) in adult subjects with schizophrenia who have completed Study SEP361-308 by the incidence of overall adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation.

Other Objectives:

- To evaluate the long-term safety and tolerability of SEP-363856 by assessing:
  - 12-lead electrocardiograms (ECG)
  - Vital sign measurements
  - Clinical laboratory tests
  - Columbia – Suicide Severity Rating Scale (C-SSRS)
  - Simpson-Angus Scale (SAS)
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)
- To evaluate the long-term 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 long-term effects of SEP-363856 on health-related quality of life as measured by the Short Form Health Survey (SF-12)
- To evaluate the long-term effects of SEP-363856 on functional capacity as measured by the Personal and Social Performance Scale (PSP)
- To evaluate long-term medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ)
- To evaluate long-term sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI)

• To evaluate the long-term impact of SEP-363856 on Healthcare Resource Utilization (HCRU)
Study Design: This is a 24-week, outpatient, multicenter, flexible-dose, open-label extension study designed to evaluate the long-term safety and tolerability of SEP-363856 (50 to 100 mg/day) for the treatment of subjects with schizophrenia who have completed Study SEP361-308 treatment period, during which they were switched from a previous antipsychotic treatment to SEP-363856. The study will consist of two periods: An open-label extension (OLE) Treatment Period (up to 24 weeks), and a Follow-up Period visit at 7 ± 2 days after last study drug dose for subjects who complete the Treatment Period and those who prematurely discontinue from the study. Subjects who meet the entry criteria and choose to enter the extension study will transition immediately at the End of Treatment (EOT) visit from Study SEP361-308. Subjects who early terminate (ET) from the SEP361-308 study are not eligible to enroll in SEP361-309. The EOT visit from Study SEP361-308 will serve as the OLE Baseline visit for the present study. Informed consent will be obtained from all subjects before any study procedures are performed for the present study. Treatment Period will occur as shown in Figure 1 Study Schematic, during which the procedures outlined in Table 2 will be conducted. Subjects will attend a Baseline visit on Day 1 (same day as the EOT visit of Study SEP361-308). Subjects will be seen at Baseline and then every 4 weeks thereafter up to Week 24. Telephone calls will be made by a qualified member of the clinical research staff to the subjects weekly between visits to administer the C-SSRS, collect AEs and concomitant medications, as well as to remind subjects about adherence to study drug administration and upcoming visits. Unscheduled visits may occur at the discretion of the investigator. Overall study design details provided in Section 7.1.
Number of Subjects (planned): This study will only enroll subjects who have completed the treatment period of Study SEP361-308 which plans to enroll approximately 120 subjects. It is anticipated that approximately 67 subjects will enroll in Study SEP361-309, assuming 75% of the subjects in Study SEP361-308 complete that study and 75% of the completers will enroll in this study.
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): To qualify for participation, subjects must meet the following key inclusion criteria: • Subject has completed the Treatment Period of Study SEP361-308. • Subject has not taken any psychotropic medication other than the study drug, pre-switch antipsychotic and protocol-allowed medications during Study SEP361-308.
Investigational Product, Dosage and Mode of Administration: SEP-363856 will be supplied as 50 mg, 75 mg and 100 mg tablets. SEP-363856 dose will be administered orally once daily at approximately the same time each evening at bedtime and may be taken without regard for food.
Duration of Treatment: 24 weeks
Reference Therapy, Dosage and Mode of Administration: Not applicable

Concomitant and Prohibited Medications:

Subjects are permitted to remain on non-prohibited psychotropic medications that have been part of their ongoing treatment regimen prior to and during SEP361-308. Other allowable psychotropic medications are discussed in Section 10.3.3.

Newly administered psychotropic medications and newly administered medications with a propensity for psychotropic effects are not permitted during the Treatment Period up through the Follow-up Visit, with the exception of the medications discussed in Section 10.3.3. The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications is not permitted during the Treatment Period.

Use of psychotropic medications after the last dose of study medication is permitted, provided they are not administered prior to the final PANSS assessment.

Subjects who are administered a psychotropic medication (other than the study drug and the acceptable medications described in Section 10.3.3) 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.

See Section 10.3 for further information on concomitant medications.

Study Endpoints:

Primary Endpoint:

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

Other Safety Endpoints:

- Observed values and changes from Baseline of Study SEP361-308 (pre-switch baseline [PS Baseline]) and Baseline of Study SEP361-309 (OLE Baseline) in clinical laboratory tests (including hematology, chemistry [including but not limited to lipid parameters and Hemoglobin A1c (HbA1c)], and urinalysis) (see Section 21)
- Observed values and changes from PS Baseline and OLE Baseline in vital signs (including temperature, body weight, body mass index [BMI], waist circumference, blood pressure [supine and standing], pulse rate [supine and standing] and respiratory rate) and 12-lead ECG parameters
- Frequency of subjects with suicidal ideation and suicidal behavior based on the C-SSRS
- Change from PS Baseline and OLE Baseline in SAS, BARS and AIMS scores
- Change from PS Baseline and OLE Baseline in PSQI scores

Other Endpoints:

- Changes from PS Baseline and OLE Baseline 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),
  - Uncorrelated PANSS (seven-factor) Score Matrix (UPSM) (positive, disorganized, negative apathy/avolition, negative deficit of expression, hostility, anxiety, and depression)
  - CGI-S score
  - CGI-I score
  - BNSS total score

- SF-12 score
- PSP score
- MSQ score

- 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 spend helping subjects per week)
- Nicotine use

Statistical Methods:

The analysis of the long-term safety and tolerability, and effectiveness will be based on the Safety population, which includes all subjects who receive at least one dose of study drug during the 24-week treatment period. All data analysis will be performed for the overall treatment group.

AEs, SAEs, and AEs leading to discontinuation will be summarized by the number and percentage of subjects with any AE, and AEs by system organ class and preferred term. AEs will be further summarized by severity and by relationship to study drug. The summary of AEs will be limited to those AEs newly occurring on or after the first dose of the OLE (SEP361-309) 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 PS Baseline and OLE Baseline (the EOT visit from Study SEP361-308) in clinical laboratory tests (including hematology, chemistry, urinalysis) and in clinical evaluations (vital signs and 12-lead ECGs) will be summarized descriptively.

The frequency of subjects with suicidal ideation and suicidal behavior based on the C-SSRS will be provided.

Descriptive statistics will be presented on the change from PS Baseline and OLE Baseline in: PANSS total score and subscale scores, CGI-S score, CGI-I score, BNSS total score, PSQI global score, SF-12 score, PSP total score, MSQ score, PANSS Marder Factor scores, and UPSM.

Sample Size:

All subjects who complete Study SEP361-308 are eligible to enroll. It is anticipated that approximately 67 subjects will enroll in this study (SEP361-309), assuming 75% of the subjects complete Study SEP361-308 and 75% of the completers will enroll in this study. The sample size is not based on statistical considerations.

Table 2: Schedule of Assessments

Procedures	**Treatment Period**							**Follow-up Period**
	V1E	**V2E**	**V3E**	**V4E**	**V5E**	**V6E**	**V7E**	**V8E**
	OLE Baseline[a]	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 EOT/ ET** [b]	**Follow-up EOS** [c]
Study Day	**Day 1**	**Day 29 ±3 days**	**Day 57 ±3 days**	**Day 85 ±3 days**	**Day 113 ±3 days**	**Day 141 ±3 days**	**Day 169 ±3 days**	**7±2 days after last dose**
Informed consent	X							
Inclusion/exclusion criteria	X							
Concomitant medication review [d]	X	X	X	X	X	X	X	X
Dispense study drug [e]	X	X	X	X	X	X		
Study drug accountability		X	X	X	X	X	X	
Telephone contacts [f]		Telephone calls to the subjects will be made at Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, and 23. Unscheduled visits may occur at the discretion of the Investigator.						
Physical/neurological examination	Core	X		X			X	X
Nicotine use information	Core			X			X	
Vital signs [g]	Core	X	X	X	X	X	X	X
Weight (including BMI [h])	Core	X	X	X	X	X	X	
Height [i]	Core Pre-switch screening							
Waist circumference	Core	X		X			X	
12-lead Electrocardiogram (ECG)	Core	X		X			X	
Hematology, chemistry, urinalysis [j]	Core	X		X			X	
Blood sample for PK [k]	Core	X		X			X	
Urine drug screen [l]		X		X			X	
Rapid urine drug screen [l]	Core							
Serum β-hCG, females only	Core							
Urine β-hCG, females only [m]		X	X	X	X	X	X	X
Rapid urine β-hCG, females only [m]	Core							
Positive and Negative Syndrome Scale (PANSS)	Core	X	X		X		X	
Clinical Global Impression – Severity (CGI-S)	Core	X	X		X		X	

Table 2: Schedule of Assessments (Continued)

Procedures	Treatment Period							Follow-up Period
	V1E	V2E	V3E	V4E	V5E	V6E	V7E	V8E
	OLE Baseline[a]	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 EOT/ ET [b]	Follow-up EOS [c]
Study Day	Day 1	Day 29 ±3 days	Day 57 ±3 days	Day 85 ±3 days	Day 113 ±3 days	Day 141 ±3 days	Day 169 ±3 days	7±2 days after last dose
Clinical Global Impression – Improvement (CGI-I)	Core	X	X		X		X	
Brief Negative Symptom Scale (BNSS)	Core	X	X		X		X	
Columbia Suicide Severity Rating Scale (C-SSRS)	Core	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS) [n]	Core	X					X	
Barnes Akathisia Rating Scale (BARS)[n]	Core	X					X	
Abnormal Involuntary Movement Scale (AIMS)[n]	Core	X					X	
Pittsburgh Sleep Quality Index (PSQI)	Core			X			X	
Personal and Social Performance Scale (PSP)	Core			X			X	
Short Form Health Survey (SF-12)	Core						X	
Medication Satisfaction Questionnaire (MSQ)	Core						X	
Healthcare Resource Utilization (HCRU), since last assessment	Pre-switch Baseline visit of Core			X			X	
Adverse events (AE) monitoring [o]	X	X	X	X	X	X	X	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; EOS = end of study; EOT = end of treatment; ET = early termination; HCRU = healthcare resource utilization; MSQ = Medication Satisfaction Questionnaire; OLE = open-label extension; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; PSP = Personal and Social Performance Scale; SAS = Simpson-Angus Scale; SF-12 = Short Form Health Survey.

[a] The Week 8 (EOT) visit of Study SEP361-308 serves as the Baseline visit for the present study. "Core" indicates assessments that were conducted at the EOS Visit of Study SEP361-308, unless otherwise indicated, and do not need to be repeated for this study.

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

[c] All subjects should 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 the 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.

[d] Medications with onset during the Core study (SEP361-308) and ongoing at the start of the current study (SEP361-309) will be entered into the eCRF.

[e] All study drug will be taken once daily in the evening at bedtime by mouth, with or without food.

[f] Telephone calls will be made by a qualified member of the research staff to the subject **weekly** between scheduled study visits to administer the C-SSRS, collect AEs and concomitant medications, as well as to remind the subject about adherence to study drug administration and upcoming visits.

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

[h] BMI will be derived in the EDC system and during statistical analysis.

[i] Height collected at the Core study (SEP361-308) Screening Visit will be re-entered into EDC at Visit 2E of this study.

[j] Subjects must be fasted (no food or drink except water at least 8 hours prior to clinical laboratory tests). A list of clinical laboratory tests is provided in Section 21.

[k] Blood samples for plasma concentrations of SEP-363856 will be collected on Day 29, Day 85 and Day 169/EOT/ET. The time and date of the previous dose of study drug prior to blood sampling and the time and date of blood sampling must be recorded. The remaining plasma samples, after PK measurement is completed, CCI

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

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

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

[o] Any new AEs occurring after signing the informed consent form for this study (SEP361-309) at V1E will be collected. Adverse events with onset during the Core study (SEP361-308) and ongoing at the start of the current study (SEP361-309) will be entered into the eCRF.

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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
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
β-hCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
BNSS	Brief Negative Symptom Scale
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
CR	Controlled release
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia – Suicide Severity Rating Scale
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
EPS	Extrapyramidal Symptoms
ET	Early Termination

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
ER	Emergency Room
FDA	U.S. Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCRU	Healthcare Resource Utilization
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
IPD	Important Protocol Deviation
IRB	Institutional Review Board
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LIMS	Laboratory Information Management System
LOCF	Last Observation Carried Forward
MCS-12	Mental Component Summary of the SF-12
MedDRA	Medical Dictionary for Regulatory Activities
MSQ	Medication Satisfaction Questionnaire
MTD	Maximum Tolerated Dose
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
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

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
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
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.
Enrolled Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Enrollment Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during baseline visit or met study requirements at baseline visit but was not dispensed study drug.
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 Visit 7E/ Week 24.
Early Termination Subject	Any subject who was successfully enrolled 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 24-week study is an open-label extension to an 8-week, outpatient, multicenter, flexible-dose, single-group study designed to evaluate the effectiveness, safety, and tolerability 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. The open-label extension will provide additional, long-term safety, tolerability and effectiveness data from subjects who completed the 8-week switch trial.

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. In an adequate and well controlled long-term, open-label extension study to Study SEP361-201, flexible treatment with SEP-363856 (25, 50, or

75 mg/day) resulted in continued improvements for up to 26 weeks in a broad array of symptoms of schizophrenia as measured by multiple effectiveness assessments.

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 long-term safety and tolerability of flexibly dosed SEP-363856 (50, 75, 100 mg/day) in adult subjects with schizophrenia who have completed Study SEP361-308 by the incidence of overall adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation.

5.2. Other Objectives

- To evaluate the long-term safety and tolerability of SEP-363856 by assessing:
  - 12-lead electrocardiograms (ECG)
  - Vital sign measurements
  - Clinical laboratory tests
  - Columbia – Suicide Severity Rating Scale (C-SSRS)
  - Simpson-Angus Scale (SAS)
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)
- To evaluate the long-term 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 long-term effects of SEP-363856 on health-related quality of life as measured by the Short Form Health Survey (SF-12)
- To evaluate the long-term effects of SEP-363856 on functional capacity as measured by the Personal and Social Performance Scale (PSP)
- To evaluate long-term medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ)
- To evaluate long-term sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI)
- To evaluate the long-term impact of SEP-363856 on healthcare resource utilization (HCRU)

6. STUDY ENDPOINTS

6.1. Primary Endpoint

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

6.2. Other Safety Endpoints

- Observed values and changes from Baseline of Study SEP361-308 (pre-switch baseline [PS Baseline]) and Baseline of Study SEP361-309 (open-label extension [OLE] Baseline) in clinical laboratory tests (including hematology, chemistry [including but not limited to lipid parameters and Hemoglobin A1c (HbA1c)], and urinalysis) (See Section 21)
- Observed values and changes from PS Baseline and OLE Baseline in vital signs (including temperature, body weight, body mass index [BMI], waist circumference, blood pressure [supine and standing], pulse rate [supine and standing] and respiratory rate) and 12-lead ECG parameters
- Frequency of subjects with suicidal ideation and suicidal behavior based on the C-SSRS
- Change from PS Baseline and OLE Baseline in SAS, BARS and AIMS scores
- Change from PS Baseline and OLE Baseline in PSQI scores

6.3. Other Endpoints

- Changes from PS Baseline and OLE Baseline 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),
  - Uncorrelated PANSS (seven-factor) Score Matrix (UPSM) (positive, disorganized, negative apathy/avolition, negative deficit of expression, hostility, anxiety, and depression)
  - CGI-S score
  - CGI-I score
  - BNSS total score
  - SF-12 score
  - PSP score
  - MSQ score
- 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 spend helping subjects per week)
- Nicotine use

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 24-week, outpatient, multicenter, flexible-dose, open-label extension study designed to evaluate the long-term safety and tolerability of SEP-363856 (50 to 100 mg/day) for the treatment of subjects with schizophrenia who have completed Study SEP361-308 treatment period, during which they were switched from a previous antipsychotic treatment to SEP-363856.

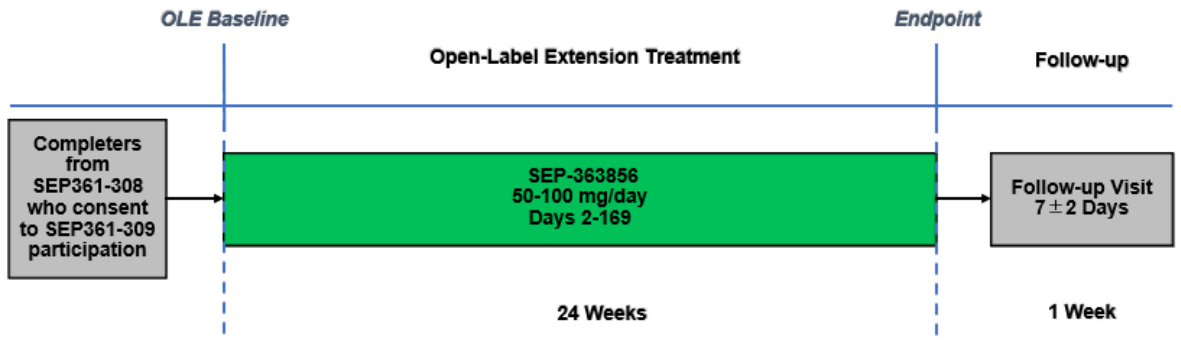
The study will consist of two periods: An open-label extension (OLE) Treatment Period (up to 24 weeks), and a Follow-up Period visit at 7 ± 2 days after last study drug dose for subjects who complete the Treatment Period and those who prematurely discontinue from the study (Figure 1).

Subjects who meet the entry criteria and choose to enter the extension study will transition immediately at the End of Treatment (EOT) visit from Study SEP361-308. Subjects who early terminate (ET) from the SEP361-308 study are not eligible to enroll in SEP361-309. The EOT visit from Study SEP361-308 will serve as the OLE Baseline visit for the present study. Informed consent will be obtained from all subjects before any study procedures are performed for the present study.

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 11.6, Study Visits and Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit at the discretion of the investigator.

Subjects will attend a Baseline visit on Day 1 (same day as the EOT visit of Study SEP361-308). Subjects will be seen at Baseline and then every 4 weeks thereafter up to Week 24. Telephone calls will be made by a qualified member of the clinical research staff to the subjects weekly between visits to administer the C-SSRS, collect AEs and concomitant medications, as well as to remind subjects about adherence to study drug administration and upcoming visits.

Figure 1: Study Schematic



Abbreviations: OLE = open-label extension.

All subjects will begin by receiving open-label SEP-363856 at the same dose they were taking upon completion of Study SEP361-308. Thereafter, the dose can be adjusted within the range of 50 to 100 mg/day, if deemed clinically necessary by the Investigator.

Dose adjustment criteria for SEP-363856 are described in Section 10.1.1.

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 EOT/ ET visit.

Safety and tolerability will be monitored throughout the study by collection of physical examination (PE) results, ECGs, vital signs, AEs, and clinical laboratory parameters. Sleep quality will be assessed using the PSQI, and suicidality will be assessed using the C-SSRS. Subjects who have any new significant findings or worsening of findings for suicidal ideation or behavior at any time during the study must be referred to the investigator for follow up evaluation.

Motor function will be assessed using the SAS, BARS and AIMS scales. HCRU will also be collected in this study.

Effectiveness will be evaluated using the PANSS total score and subscale scores, as well as CGI-S score and CGI-I score, BNSS score, and PSQI global scores. Function, quality of life, and treatment satisfaction will be assessed using the PSP, SF-12, and MSQ.

Population pharmacokinetic (POPPK) analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately.

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

This is an open-label extension study to further evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (50, 75 or 100 mg) over 24 weeks of treatment in subjects with schizophrenia who completed Study SEP361-308. Long-term effectiveness of SEP-363856 will also be evaluated.

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 the 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 Endpoints

The objective of this study is to demonstrate that clinically stable outpatients with schizophrenia who have completed a switch from their current antipsychotic treatment can be safely and effectively maintained on open-label treatment with SEP-363856 for a period of 24 weeks. The outcome measures include standard safety measures (eg, AE's, SAE's, measures of motor function, assessment of suicidality, laboratory assessments, and ECGs). Additional validated effectiveness assessments for schizophrenia (eg, PANSS, CGI-S) that were also employed in Phase 2 and Phase 3 studies of SEP-363856 are included for the purpose of providing longer-term effectiveness data. Additionally, measures assessing function, 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.
- Telephone calls will be made by a qualified member of the clinical research staff to the subjects weekly between visits that are more than one week apart to administer the C-SSRS, collect AEs and concomitant medications, as well as to remind subject about adherence to study drug administration and upcoming visits (Section 11.6.8).
- 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 and be able to comply with the protocol, in the opinion of the investigator. Separate consent will be obtained from a caregiver or legal guardian if required by local law.
2. Subject has completed the Treatment Period of Study SEP361-308.
3. Subject has not taken any psychotropic medication other than the study drug, pre-switch antipsychotic and protocol-allowed medications described in Section 10.3.3 during Study SEP361-308.
4. Female subject must have a negative rapid urine pregnancy test at the End of Treatment (EOT) Visit of Study SEP361-308.
5. 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. Contraception requirements are detailed in Section 10.4.
6. Male subjects must agree to avoid fathering a child and use acceptable effective methods of birth control from screening in Study SEP361-308, until at least 30 days after the last study drug administration in the present study (SEP361-309). Contraception requirements are detailed in Section 10.4.

8.2. Subject Exclusion Criteria

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

1. Subject answered "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 the EOT Visit of Study SEP361-308. Subjects who answered "yes" to either of these questions must be referred to the Investigator for follow-up evaluation.
2. Subject has a clinically significant abnormality including physical examination (PE), vital signs, or ECG (based on investigator read) finding at the EOT Visit of Study SEP361-308 that the Investigator considers to be inappropriate to allow participation in the study.
3. Subject has a positive rapid urine drug screen (UDS) at the EOT Visit of Study SEP361-308. However, a positive UDS test performed locally at the site may not result in exclusion of subjects if the Investigator determines that the positive test is a result of prescription medicine(s) other than cannabinoids; subjects with a positive UDS for cannabinoids may not be automatically excluded if a documented investigator clinical assessment (forwarded to the Medical Monitor) determines 1) that their symptoms are clinically stable, 2) that they are counselled that continued use of cannabinoids is prohibited, and 3) that they commit to abstinence for the remainder of the study.

4. Female subject is pregnant or lactating.
5. Subject is at high risk of non-compliance in the Investigator's opinion.
6. 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°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 enrollment and subject visits. 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 cards (Medication Number[s].) 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 quantities 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

All subjects will begin by receiving open-label SEP-363856 at the same dose they were taking upon completion of Study SEP361-308. Thereafter, the dose can be adjusted within the range of 50 to 100 mg/day, if deemed clinically necessary by the Investigator.

Dose increases are to be made in increments of 25 mg (up to a maximum dose of 100 mg/day) no more frequently than weekly if the response to the previous dose level is not adequate and there are no significant tolerability problems, based on Investigator judgment. Increases in SEP-363856 dose will occur at regularly scheduled study visits, when possible. Dose increases between regularly scheduled visits may occur; however, the subject must return to the clinic for an unscheduled visit for drug dispensation (see Section 11.6.10).

The SEP-363856 dose can be decreased at any time in 25 mg increments 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 11.6.10).

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. Concomitant Medications

Concomitant medications in SEP361-308 that were ongoing at the EOT Visit of Study SEP361-308 will be entered into the electronic case report form (eCRF) for this study (SEP361-309). All changes in concomitant medications or new medications administered during the study up to the Follow-up Visit will be recorded.

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

Information on the format and version of 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. Prohibited Medications

Newly administered psychotropic medications and newly administered medications with a propensity for psychotropic effects are not permitted during the Treatment Period up through the Follow-up Visit, with the exception of the medications discussed in Section 10.3.3. The use of herbal supplements, dietary supplements or other complementary or alternative medications for treating psychiatric indications is not permitted during the Treatment Period; however, is permitted after the last dose of study medication provided, they are not administered prior to the final PANSS assessment.

Use of psychotropic medications after the last dose of study medication is permitted provided, they are not administered prior to the final PANSS assessment.

Subjects who are administered a psychotropic medication (other than the study drug and the acceptable medications described in Section 10.3.3) 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.

10.3.2. Prohibited Therapies

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

10.3.3. Allowed Concomitant Psychotropic Medications

Subjects are permitted to remain on non-prohibited psychotropic medications that have been part of their ongoing treatment regimen prior to and during SEP361-308. Treatment with benztropine (benzotropine outside the US) up to 6 mg/day is permitted, as needed, for motor symptoms. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with propranolol (up to 120 mg/day) is permitted as needed for akathisia. These allowed medications for the treatment of EPS and akathisia may be given in any formulation (oral, intramuscular [IM] or intravenous [IV]) as deemed appropriate by the investigator. Medications used to treat motor symptoms should not be given prophylactically.

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 ≤ 10 mg/day may be administered at bedtime for insomnia, as needed. Over-the-counter melatonin may 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 non-prohibited 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.

10.3.4. Concomitant Non-psychotropic Medications

Non-psychotropic medications may be used to treat mild, chronic medical conditions. This includes β-adrenergic antagonists used to treat stable hypertension. Routine vaccines (ie, Coronavirus Disease 2019 [COVID-19], seasonal influenza, pneumonia, 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 10.5.

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 or confirmed by follicle stimulating hormone (FSH) from SEP361-308 concentrations within postmenopausal range as determined by the central laboratory

-OR-

- Childbearing potential with a negative pregnancy test performed at the End of treatment (EOT) Visit of Study SEP361-308 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®);
    - Injectable hormonal contraception (such as medroxyprogesterone acetate injection);
    - Oral or transdermal hormonal contraception.
    - Vaginal ring (eg, NuvaRing®).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system.

- 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 in Study SEP361-308 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.

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) and medical and psychiatric history collected in the core study (SEP361-308) will be utilized for this study. Year of birth, age and sex will be re-entered into the eCRF of this study.

11.2. Prior and Concomitant Medication Review

See Section 10.3 for a complete description of medications permitted during the study. Concomitant medications in SEP361-308 that were ongoing at the EOT Visit will be re-entered into the eCRF for this study (SEP361-309). All changes in concomitant medications or new medications administered during the study up to the Follow-up Visit will be recorded.

At a minimum the following parameters will be recorded for all concomitant medications: medication name, dose, frequency, route, start date and time, stop date and time, and indication.

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

11.3. 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 study Baseline or subsequently during study conduct.

11.3.1. 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.

11.3.2. Clinical Laboratory Tests

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

Blood and urine samples will be collected for clinical laboratory tests. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

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

Any clinically significant changes in laboratory assessments from signing of the informed consent form, as determined by the Investigator, will be noted as AEs in the CRF.

11.3.3. 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 collected in the core study (SEP361-308) at Visit 1 (Screening) will be re-entered into the eCRF at Visit 2E of this study. Weight will be measured in street clothes, without shoes and coat/jacket. BMI for all 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.

Any clinically significant vital sign abnormalities from signing of the informed consent form (ICF), as determined by the Investigator, will be noted as AEs in the CRF.

11.3.4. 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 signing of the ICF, 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.

11.3.5. 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.

Any clinically significant changes in PE and neuro exam findings from signing of the ICF, as determined by the Investigator, will be noted as AEs in the CRF.

11.3.6. Safety Scales

When applicable, raters will receive training regarding each safety scale prior to performing them.

11.3.6.1. 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.

11.3.6.2. 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.

11.3.6.3. 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.

11.3.6.4. 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. For all visits, 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.

11.3.6.5. 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 oversight from the site.

11.4. Effectiveness Assessments

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

11.4.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 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.

11.4.2. 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.

11.4.3. 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.

11.4.4. 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.

11.4.5. 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, 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.

11.4.6. 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.

11.4.7. 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 (Vernon-2010). The subject will be asked the following question:

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

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

(1) Extremely dissatisfied

(2) Very dissatisfied

(3) Somewhat dissatisfied

(4) Neither dissatisfied nor satisfied

(5) Somewhat satisfied

(6) Very satisfied

(7) Extremely satisfied

11.4.8. Healthcare Resource Utilization

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

- number of physician office visits, ER 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)

11.4.9. 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.

11.5. 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 must be recorded. Plasma SEP-363856 concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SEP-363856 exposure will be explored using population PK/pharmacodynamics (PD) methods and reported

separately. See Section 22, Appendix III for details including instructions of processing blood samples for plasma.

Plasma samples collected for PK concentration analysis [redacted]

11.6. Study Visits and Assessments

See Table 2, for a summary of procedures at each study visit. See Section 11.1 to Section 11.6.10 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.

1. PANSS
2. BNSS
3. C-SSRS
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.

11.6.1. Visit 1E: Open-Label Extension Baseline (Day 1) – Treatment Period

Visit 1E (Open-label Baseline visit) of the present study is on the same day as the EOT Visit of Study SEP361-308. Subjects will be evaluated at this visit to determine their eligibility for the study. 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.
- Review inclusion and exclusion criteria
- Concomitant medication review
- Adverse events monitoring
- Dispense study drug

The following procedures conducted in the Core study (SEP361-308) EOT Visit do not need to be repeated for the Open-label extension Baseline visit of this study (SEP361-309):

- Physical and neurological examinations
- Collect nicotine use information
- Vital sign measurements
- Weight (including BMI)
- Waist circumference
- 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)
- Blood sample for PK
- Blood sample for pregnancy test (β-hCG) for female subjects
- Urine sample for UDS and rapid urine drug screen
- Urine sample for rapid urine pregnancy testing
- PANSS
- BNSS
- CGI-S
- CGI-I
- C-SSRS
- SAS
- BARS
- AIMS
- PSQI
- PSP
- SF-12
- MSQ
- HCRU

11.6.2. Visit 2E (Week 4; Day 29 ± 3) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Physical and neurological examinations
- 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 PK
- Urine sample for urinalysis, UDS, and β-hCG (for female subjects)
- PANSS
- CGI-S
- CGI-I
- BNSS
- C-SSRS
- SAS
- BARS
- AIMS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.6.3. Visit 3E (Week 8; Day 57 ± 3) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- Weight (BMI derived in the electronic data system)
- Urine sample for β-hCG (for female subjects)
- PANSS
- CGI-S
- CGI-I
- BNSS
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.6.4. Visit 4E (Week 12; Day 85 ± 3 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Physical and neurological examinations
- Collect nicotine use information
- Vital sign measurements
- Weight and waist circumference (BMI derived in the electronic data system)
- 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology and serum chemistry)
- Blood sample for PK
- Urine sample for pregnancy test (β-hCG) for female subjects
- Urine sample for UDS
- C-SSRS
- PSQI
- PSP
- HCRU
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.6.5. Visit 5E (Week 16; Day 113 ± 3 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- Weight (BMI derived in the electronic data system)
- Urine sample for β-hCG (for female subjects)
- PANSS
- CGI-S
- CGI-I
- BNSS
- C-SSRS

- Collect adverse events
- Study drug accountability
- Dispense study drug

11.6.6. Visit 6E (Week 20; Day 141 ± 3 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Vital sign measurements
- Weight (BMI derived in the electronic data system)
- Urine sample for β-hCG (for female subjects)
- C-SSRS
- Collect adverse events
- Study drug accountability
- Dispense study drug

11.6.7. Visit 7E (Week 24 / End of Treatment / Early Termination; Day 169 ± 3 days) – Treatment Period

The following procedures will be conducted during this visit:

- Collect concomitant medications
- Physical and neurological examinations
- Collect nicotine use information
- 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 PK
- Urine sample for urinalysis, UDS, and β-hCG (for female subjects)
- PANSS
- CGI-S
- CGI-I
- BNSS
- C-SSRS

- SAS
- BARS
- AIMS
- PSQI
- PSP
- SF-12
- MSQ
- HCRU
- Collect adverse events
- Study drug accountability

11.6.8. Telephone Contact (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, and 23) – Treatment Period

Telephone calls will be made by a member of the research staff to the subject between scheduled study visits at Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, and 23. The telephone calls will be used to administer the C-SSRS, collect AEs and concomitant medications, as well as to remind the subject about adherence to study drug administration and upcoming visits.

11.6.9. Visit 8E (7 ± 2 days after last dose) - Follow-up Period

All subjects who discontinue early or complete the study will have a safety follow-up visit 7 ± 2 days after their last dose of study drug. While every effort should be made to complete the Follow-up Visit in the clinic, administration of the 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 β-hCG (for female subjects)
- C-SSRS
- Adverse events

11.6.10. 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.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

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

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

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from the signing of the ICF to the last study visit (including Follow-up Visit).

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

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 (ER) 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 signing of the ICF 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. If a clinically significant laboratory or ECG abnormality is found 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 stop taking 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 24), every effort should be made to complete the final evaluation procedures, in accordance with the ET visit described in Section 11.6.7.

Subjects who complete the study 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 11.6.9.

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 of the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects will undergo final evaluation procedures in accordance with the early termination (ET) visit described in Section 11.6.7 and safety Follow-up Visit as described in Section 11.6.9.

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

All subjects who complete SEP361-308 are eligible to enroll. It is anticipated that approximately 67 subjects will enroll in this study (SEP361-309), assuming 75% of the subjects complete Study SEP361-308 and 75% of the completers will enroll in this study. The sample size is not based on statistical considerations.

15.2. Analysis Populations

15.2.1. Safety Population

The safety population will consist of all subjects who receive at least one dose of study drug during the 24-week OLE treatment period. The Safety Population will be used for the long-term safety, tolerability, and effectiveness analyses.

15.3. Data Analysis

Descriptive statistics will be compiled for all endpoints for the overall treatment group.

15.3.1. Subject Disposition

Subject disposition will be summarized and presented for the number and percentage of subjects who entered the extension study, received at least one dose of the open-label extension study drug, and completed or discontinued from the open-label extension treatment period (including reasons for discontinuation).

15.3.2. Study Drug Exposure and Compliance

Duration of exposure and compliance during the open-label extension treatment period will be summarized for the safety population.

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

- Number and percentage of subjects with the open-label extension study drug exposure ≥ 1, ≥ 14, ≥ 28, ≥ 42, ≥ 90, ≥ 120, ≥ 150 days;
- Number and percentage of subjects with the open-label extension study drug exposure for 1 - 13, 14 - 27, 28 - 41, 42 - 89, 90 - 119, 120 - 149, ≥ 150 days

Percent compliance will be calculated overall for the open-label extension treatment period as: (number of tablets taken / number of tablets should have been taken) × 100%. Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the open-label extension 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 entire open-label extension 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 open-label extension 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

Demographic and baseline characteristics data will be summarized for the safety population. Selected data (eg, PANSS total score, CGI-S score, etc.) will be summarized at both the pre-switch (PS) Baseline of Study SEP361-308 and the open-label extension (OLE) Baseline of Study SEP361-309.

Medical history data collected at the entry into studies SEP361-308 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 collected at the entry into Study SEP361-308 will also be summarized for the safety population.

15.3.5. Effectiveness Analyses

Effectiveness data will be summarized descriptively for the safety population.

The observed values of PANSS total score and subscale scores (positive, negative, and general psychopathology), PANSS Marder Factor (five-factor) scores, Uncorrelated PANSS (seven-factor) Score Matrix (UPSM), CGI-S score, CGI-I, BNSS total score, SF-12 score, PSP score, and MSQ score, at the PS Baseline, OLE Baseline, and each scheduled post-OLE Baseline extension visit, including the Week 24 last-observation carried forward (LOCF) endpoint, will be summarized descriptively. Changes from Baseline in these efficacy measures will be summarized at each scheduled post-OLE Baseline extension visit and Week 24 LOCF endpoint, based on both the PS Baseline and the OLE Baseline.

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

The proportion of subjects who achieve a response, defined as a 20% or greater improvement (ie, decrease) in PANSS total score from the Baseline, will be calculated for each scheduled visit and the Week 24 LOCF endpoint based on the PS Baseline of study SEP361-308.

15.3.5.1. 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 PS Baseline, OLE Baseline, and each scheduled extension visit will be summarized, as well as the average length of hospital stays (for any reason and those related to schizophrenia) at these time points. The frequency and percentage of subjects receiving unpaid care at PS Baseline, OLE Baseline, and each scheduled extension visit, along with the average number of hours a caregiver spends per week helping the subject at these time points, 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 the PS Baseline and from the OLE Baseline at each scheduled extension visit will be summarized. Shifts from the PS Baseline and from the OLE Baseline to each scheduled extension visit in whether the subject receive unpaid care will also be summarized.

15.3.5.2. Nicotine Use Information

Nicotine use data will be summarized descriptively at each visit that it is scheduled for collection. 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 PS Baseline, OLE Baseline, and each scheduled post-OLE Baseline extension visit are not in opposite directions, a subject's overall nicotine consumption at each scheduled post-OLE Baseline extension 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 PS Baseline, OLE Baseline, or each scheduled post-OLE Baseline visit or at more than one of these time point, the amount of cigarette used per day and the change from Baseline values will be summarized at each scheduled post-OLE Baseline extension visit, based on both the PS Baseline and the OLE Baseline.

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

15.3.5.3. Adjustment for Multiplicity

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

15.3.6. Safety Analyses

15.3.6.1. Analysis of Primary Endpoint

The primary endpoint is the incidence of overall AEs, SAEs, and AEs leading to discontinuation. The incidence will be calculated by a proportion consisting of the number of subjects who experience these events (ie, AEs, SAEs, and AEs leading to discontinuation) as the numerator over the safety population as the denominator along with a corresponding 95% confidence interval (CI).

15.3.6.2. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

The summary of AEs for the current study will be limited to those AEs newly occurring on or after the first dose of the OLE (SEP361-309) study drug. AEs carried over from study SEP361-308 will be presented in data listings only.

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 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. All AEs starting after the last dose of OLE 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.

15.3.6.3. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables and through by visit summaries of the observed values including the Week 24 LOCF endpoint along with change from Baseline values. Both the PS Baseline and the OLE Baseline will be used in the calculation of change 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-OLE Baseline for selected parameters will also be presented. PCS criteria for clinical laboratory parameters will be provided in the statistical analysis plan (SAP).

15.3.6.4. ECGs

ECG analysis will be based on the centrally read data. Observed values and changes from Baseline in ECG parameters will be summarized. 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. Both the PS Baseline and the OLE Baseline will be used in the calculation of change values.

15.3.6.5. Vital Signs

Vital sign parameters will be summarized by presenting by visit and Week 24 LOCF endpoint summaries of the observed values and the change from Baseline values. Both the PS Baseline and the OLE Baseline will be used in the calculation of change values. For adolescent subjects, height will also be summarized. In addition, the number and percentage of subjects with at least one PCS value post-OLE 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-OLE Baseline period, as well as by visit.

15.3.6.6. Physical and Neurological Examination

Clinically significant findings from the physical and neurological examination at the extension visits will be captured as AEs as appropriate and summarized together with the other AEs.

15.3.6.7. Concomitant Medications

All medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical) 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 open-label extension study, with a start date/time on or after the first dose of the open-label extension study drug and on or before the last dose of the open-label extension study drug; or with a start date/time prior to, and an end date/time on or after, the first dose of the open-label extension study drug, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the first dose of the open-label extension study drug will be considered prior medications. Medications that started after the last dose of the open-label extension 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.

15.3.6.8. 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-OLE Baseline period, by visit, and by telephone contact week.

15.3.6.9. Measures of Motor Function

Measures of motor function include SAS, BARS and AIMS. The observed values of SAS mean score, BARS total score and AIMS total score at the PS Baseline, OLE Baseline, and each scheduled post-OLE Baseline extension visit that it is scheduled for collection, including the Week 24 LOCF endpoint, will be summarized. Changes from Baseline in these measures will also be summarized for each scheduled post-OLE Baseline extension visit, using both the PS Baseline and the OLE Baseline.

15.3.6.10. Pittsburgh Sleep Quality Index

Observed PSQI global score at the PS Baseline, OLE Baseline, and each scheduled post-OLE Baseline extension visit that it is scheduled for collection, including the Week 24 LOCF endpoint, will be summarized. Changes from Baseline in PSQI global score will also be summarized for each scheduled post-OLE Baseline extension visit, based on both the PS Baseline and the OLE Baseline.

15.3.6.11. 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.

15.3.7. 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 POP-PK/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 24 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 data collected during the study (except clinical laboratory test results, ECG results, POPPK and some scales) will be recorded in the subject's eCRF. 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 food and drug administration (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
Inclusion/exclusion criteria	A
Concomitant medication review	A
Dispensation of study drug	F
Study drug accountability	A, F
Telephone Contacts	A
Physical and neurological examination	A
Nicotine use information	A
Vital signs	A
Weight (including BMI)	A
Height	A
Waist circumference	A
12-lead Electrocardiogram (ECG)	B
Hematology, chemistry, and urinalysis	G
Blood sample for PK	C
Urine drug screen	G
Rapid urine drug screen	A
Serum β-hCG, females only	G
Urine β-hCG (females)	G
Rapid urine β-hCG, females only	A

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

Protocol Step	Computerized System Type or Description
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
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
Pittsburgh Sleep Quality Index (PSQI)	D
Personal and Social Performance Scale (PSP)	D
SF-12	D
Medication Satisfaction Questionnaire (MSQ)	D
Healthcare Resource Utilization (HCRU)	D
Pretreatment/Adverse events (AE) monitoring	A

A = EDC (Medidata RAVE); B =ECG central vendor; C = LIMS/ American Standard Code for Information Interchange (ASCII); D = Signant Health; F = Randomization and Trial Supply Management System (RTSM); G = Central Laboratory.
Abbreviations: EDC = electronic data capture; LIMS = laboratory information management system.

16.3. Study Monitoring

This study will be monitored using a risk-based approach from initiation to completion by the Sponsor or its representative. Monitoring will 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 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, 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 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 IRB/ 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.

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 (EOS). 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, SEP361-309, Version 3.00 "An Open-label Extension Study to Assess the 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 over-read will be retained at the study center.

4. Data Standardization

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

21. APPENDIX II. CLINICAL LABORATORY TESTS

Detailed instructions will be provided in a study center manual.

The following clinical laboratory tests are to be performed.

Clinical Safety Panel

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

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Cholesterol, Creatinine, Creatinine clearance (calculated GFR), 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

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)

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.

22. APPENDIX III. 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 29	Anytime (Actual date and clock time will be recorded)	6 mL
Day 85	Anytime (Actual date and clock time will be recorded)	6 mL
Day 169 / EOT / ET	Anytime (Actual date and clock time will be recorded)	6 mL