SEP-363856

Clinical Study Protocol SEP361-202

A 26-Week Open-label Safety and Tolerability Extension Study of SEP-363856 in Adult Subjects with Schizophrenia

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	Head of Global Clinical Development, Psychiatry Sunovion Pharmaceuticals Inc.	Telephone: Email:
Medical Monitor	Medical Director Global Therapeutic QuintilesIMS Inc.	Office: Mobile: Email:
SAE/Pregnancy Reporting	PPD Pharmacovigilance (PVG)	Hotline Number: Fax: Email:

1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals, Inc.

Name of Investigational Product: SEP-363856

Title of Study: A 26-Week Open-label Safety and Tolerability Extension Study of SEP-363856 in Adult Subjects with Schizophrenia

Proposed Indication: Schizophrenia

Study Centers: Approximately 35 centers that have participated in Study SEP361-201

Phase of Development: 2

Study Objectives:

Primary: The primary objective of this study is to evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (25, 50, or 75 mg/day [ie, once daily]) in adult subjects with schizophrenia who have completed Study SEP361-201 by the incidence of overall adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation.

Secondary:

- To evaluate the long-term safety and tolerability of SEP-363856 by assessing vital signs, physical examinations (PE), body weight and body mass index (BMI), 12-lead electrocardiograms (ECG), clinical laboratory evaluations, and suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)
- To evaluate the long-term effectiveness of SEP-363856 using the Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression-Severity (CGI-S), PANSS subscale scores (positive, negative, general psychopathology), Brief Negative Systems Scale (BNSS), and Montgomery-Asberg Depression Rating Scale (MADRS)
- To explore the long-term maintenance of response in subjects treated with SEP-363856 as measured by the time to relapse and the rate of relapse

Other:

- To assess whether long-term treatment with SEP-363856 is associated with extrapyramidal symptoms as measured by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS)
- To characterize the long-term effects of SEP-363856 as measured by the Drug Effects Questionnaire (DEQ)
- To characterize the subjective long-term effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI)
- To explore the effects of SEP-363856 on cognition as assessed by the CogState Brief Battery (CBB) and the CogState Schizophrenia Battery (CSB)
- To explore the effects of SEP-363856 on functional outcomes as measured by the UPSA-B total score

Study Design:

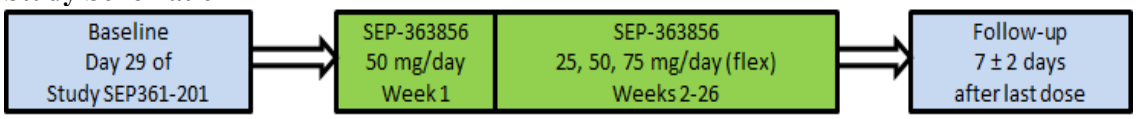
This is a 26-week, multiregional, open-label extension study designed to evaluate the long-term safety and tolerability of SEP-363856 for the treatment of subjects with schizophrenia who have completed

the 4-week double-blind treatment phase of Study SEP361-201.

Subjects who meet the entry criteria will transition immediately from Study SEP361-201 (at Visit 7; assessments performed at Study SEP361-201 Visit 7 will serve as the Baseline assessments for the present study). Informed consent will be obtained from all subjects before any study procedures are performed for the present study.

Subjects will attend an initial visit on Day 1 (same day as Visit 7 of study SEP361-201). Subjects may be hospitalized for the first week of the present study, if deemed appropriate by the Investigator. During the treatment period, clinic visits will occur as shown in the following figure, during which the procedures outlined in Table 2 will be conducted. Subjects will be seen at weekly intervals for the first 4 weeks, then every 4 weeks thereafter up to week 26. Telephone calls will be made by a member of the clinical research staff to the subjects between scheduled study visits (between Weeks 1 and 2, and at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25) to monitor clinical symptoms and adverse events. If subject appears to be symptomatic, an unscheduled visit will be made as early as possible. Subjects who discontinue early from the study or complete study will be required to complete the follow-up visit 7 days (± 2 days) post last dose of study drug.

Study Schematic



26 Weeks Open-label

Note: Titration up to 75 mg/day is permitted (but not required) on Day 4 for reasons of efficacy as an unscheduled visit.

All subjects will receive open-label SEP-363856 50 mg/day from Day 1 through Day 3. Beginning on Day 4, flexible dosing ranging from 25 to 75 mg/day is permitted, if deemed clinically necessary (for reasons of safety, tolerability, or efficacy) by the Investigator. On Day 4, subjects are permitted (but not required) to titrate up to 75 mg/day for reasons of efficacy. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits based on Investigator judgement. Day 4 dosing changes will occur at an unscheduled visit. Thereafter, an increase in dose should occur at weekly intervals in increments of one dose level at a time to a maximum dose of 75 mg/day. Dose reduction for tolerability purposes is allowed at any time during the study.

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

Subjects who meet any discontinuation/withdrawal criteria will be terminated from the study. Upon termination from the study, hospitalization will be allowed for up to 7 days to stabilize the subject, if necessary. Prior authorization for hospitalization must be approved by the Medical Monitor.

Effectiveness will be evaluated using the PANSS total and subscale scores, as well as CGI-S, BNSS, and MADRS scores.

Subjects will provide information on subjective drug effects via administration of the DEQ. In addition, effects on movement disorders will be measured using the AIMS, BARS and SAS scales. Subjective effects on sleep will be measured by the PSQI scale. Effects on cognition will be assessed by the Cogstate Brief Battery (CBB) and the CogState Schizophrenia Battery (CSB), and a functional

outcome measure (UPSA-B total score).

Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected at Visit 2E, 5E, 8E, and 11E. Population pharmacokinetic (POPPK) analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately.

Inclusion and Exclusion Criteria:

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 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 Study SEP361-201 through Week 4.
3. Subject has not taken any medication other than the study drug for the purpose of controlling schizophrenia symptoms during Study SEP361-201.
4. Female subject must have a negative urine pregnancy test at Visit 7 of Study SEP361-201; females who are post-menopausal (defined as at least 12 months of spontaneous amenorrhea) and those who have undergone hysterectomy or bilateral oophorectomy will be exempted from the pregnancy test. Female subject of reproductive potential agrees to remain abstinent or use highly effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken (See Section 21 Appendix II Highly Effective Contraceptive procedures). In the Investigator's judgment, the subject will adhere to this requirement.
5. Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use highly effective methods of birth control from screening until at least 30 days after the last study drug administration.

Exclusion Criteria:

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

1. Subject answers “yes” to “suicidal ideation” Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Visit 7 of Study SEP361-201. Subjects who answer “yes” to this question must be referred to the Investigator for follow-up evaluation.
2. Subject has a clinically significant abnormality including physical examination, vital signs, ECG, or laboratory test at Visit 7 of Study SEP361-201 that the investigator in consultation with the medical monitor considers to be inappropriate to allow participation in the study.
3. Subject has a positive urine drug screen (UDS) or breath alcohol test at Visit 7 of Study SEP361-201.
4. 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.

Investigational Product, Dosage and Mode of Administration:

SEP-363856 treatment will be size 0, Swedish-orange capsules (25, 50, or 75 mg/day) administered orally once daily. Study drug may be taken with or without food at approximately the same time each evening before bed-time.

All subjects will be flexibly dosed with SEP-363856 at 25, 50, or 75 mg/day, provided as open-label patient packs.

Duration of Treatment: 26 weeks

Reference Therapy, Dosage and Mode of Administration:

Not applicable.

Concomitant Medications:

Concomitant Non-psychotropic Medications:

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

Concomitant Psychotropic Medications:

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

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

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

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

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

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

In regions that do not have the specified drugs available, similar drugs at equivalent dosages will be

permitted as described in the Operations Manual or in consultation with the Medical Monitor.

Subjects should abstain from alcohol through the end of the study.

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

Criteria for Evaluation:

Primary Endpoints:

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

Secondary Endpoints:

- Absolute values and changes from double-blind (DB) Baseline of Study SEP361-201 and open-label (OL) Baseline of Study SEP361-202 in clinical laboratory tests (hematology, serum chemistry, urinalysis, glucose and lipid panel, prolactin, glycosylated hemoglobin (HbA_{1c})
- Absolute values and changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in clinical evaluations (vital signs body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], 12-lead ECGs)
- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS
- Rate of relapse and time to relapse during the 26-week OL period for subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856. Relapse will be defined as the onset of any of the following:
  - An increase in PANSS total score ≥ 30% from the PANSS total score at clinical response and a CGI-S score ≥ 3;
  - Re-hospitalization for worsening of psychosis;
  - Emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others.
- Changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in PANSS total score and subscale scores (positive, negative, and general psychopathology)
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in CGI-S score.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in BNSS total score.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in MADRS total score.
- Proportion of subjects who achieve a response, defined as a 20% or greater improvement in PANSS total score from the baseline, and calculated using (1) the DB Baseline of Study SEP361-201 for subjects assigned to double-blind SEP-363856, and (2) the OL Baseline of Study SEP361-202 for subjects assigned to double-blind placebo.

Other Endpoints:

- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in BARS, AIMS and SAS scores.
- Absolute visual analogue scale (VAS) scores of the DEQ.

- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in PSQI score.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of SEP361-202 in CBB composite score
- Change from Week 12 of Study SEP361-202 in CSB composite score at Week 26
- Change from OL Baseline of Study SEP361-202 in UPSA-B total score

Statistical Methods:

The analysis of the long-term safety and tolerability, and efficacy will be based on the safety population, which includes all subjects who receive at least one dose of study drug during the 26-week OL extension period.

The primary analysis for the study is to assess the incidence of AEs, SAEs, and AEs leading to discontinuation. 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 AE occurring on or after the first dose (of the 26-week OL extension period) of study drug.

Absolute values and changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in clinical laboratory tests (hematology, serum chemistry, urinalysis, glucose and lipid panel, prolactin, glycosylated hemoglobin (HbA_{1c})) and in clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], 12-lead ECGs) will be summarized descriptively. Changes in physical examinations will also be summarized descriptively. The frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS will be provided.

Clinical response to 4 weeks of treatment with SEP-363856 is defined as meeting both of the following criteria: (1) a decrease in PANSS total score of $\geq 20\%$ from baseline, and (2) a CGI-S score ≤ 4. For subjects assigned to double-blind SEP-363856, clinical response will be evaluated using the Day 29 data of study SEP361-201, against the DB baseline of study SEP361-201. For subjects assigned to double-blind placebo, clinical response will be evaluated using the Day 29 data of study SEP361-202, against the OL baseline of study SEP361-202.

Relapse will be identified programmatically using the pre-defined criteria among subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856. The rate of relapse will be calculated as the proportion of subjects with a relapse in the 26-week OL extension period, along with the 95% confidence interval. The time-to-relapse will be summarized descriptively and will also be presented by a Kaplan-Meier plot.

Descriptive statistics will be presented on the change in PANSS total and subscale scores, change in CGI-S score, change in BNSS total score, and change in MADRS total score. Changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 will be presented. The proportion of subjects who achieve a response, defined as a 20% or greater improvement in PANSS total score from the baseline, and calculated using (1) the DB Baseline of Study SEP361-201 for subjects assigned to double-blind SEP-363856,and (2) the OL Baseline of Study SEP361-202 for subjects assigned to double-blind placebo, will be calculated.

Sample Size: All subjects who complete the 4-week double-blind treatment period of Study SEP361-201 are eligible to enroll. It is anticipated that approximately 180 subjects will enter this open-label extension study.

Table 2: Schedule of Assessments

Study Visit Number **Study Visit Week**	**Visit 1E[a]** **Baseline**	**Visit 2E** **Week 1**	**Visit 3E** **Week 2**	**Visit 4E** **Week 3**	**Visit 5E** **Week 4**	**Visit 6E** **Week 8**	**Visit 7E** **Week 12**	**Visit 8E** **Week 16**	**Visit 9E** **Week 20**	**Visit 10E** **Week 24**	**Visit 11E** **Week 26 or ET[b]**	**Visit 12E** **Week 27** **Follow-up[c]** **EOS**
Study Visit Day	**1**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**190 ± 2**
Obtain informed consent	X											
Review inclusion/exclusion criteria	X											
Dispense study drug[d]	X[m]	X	X	X	X	X	X	X	X	X		
Study drug accountability		X	X	X	X	X	X	X	X	X	X	
Telephone Contacts[e]		Telephone calls to the subjects will be made between Weeks 1 and 2 and at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25. If subject appears to be symptomatic, an unscheduled visit will be made as early as possible.[f]										
Clinical and Laboratory Evaluations												
Adverse event (AE) monitoring	↑ Performed at Visit 7 of study SEP361-201 ↓	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication review		X	X	X	X	X	X	X	X	X	X	X
Physical and neurological examination					X	X		X			X	
Vital signs[g]		X		X	X	X	X	X	X	X	X	X
Weight (including BMI)		X		X	X	X	X	X	X	X	X	
Waist circumference		X		X	X	X	X	X	X	X	X	
Electrocardiogram (ECG)		X			X	X	X	X	X	X	X	
Clinical laboratory tests[h]		X			X			X			X	
Blood sample for POPPK[i]		X			X			X			X	
Urine drug screen[j]		X			X			X			X	
Urine β-hCG[k]		X	X	X	X	X	X	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)		X	X	X	X	X	X	X	X	X	X	

Table 2: Schedule of Assessments (Continued)

Study Visit Number **Study Visit Week**	**Visit 1E[a] Baseline**	**Visit 2E Week 1**	**Visit 3E Week 2**	**Visit 4E Week 3**	**Visit 5E Week 4**	**Visit 6E Week 8**	**Visit 7E Week 12**	**Visit 8E Week 16**	**Visit 9E Week 20**	**Visit 10E Week 24**	**Visit 11E Week 26 or ET[b]**	**Visit 12E Week 27 Follow-up[c] EOS**
Study Visit Day	**1**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**190 ± 2**
Brief Negative Symptoms Scale (BNSS)		X	X	X	X	X	X	X	X	X	X	
Clinical Global Impression – Severity (CGI-S)		X	X	X	X	X	X	X	X	X	X	
Montgomery-Asberg Depression Rating Scale (MADRS)		X	X	X	X	X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X	X	X	X	X	X	X
Drug effects questionnaire (DEQ)											X	X
Abnormal Involuntary Movement Scale (AIMS)[1]		X	X	X	X	X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)[1]		X	X	X	X	X	X	X	X	X	X	
Simpson-Angus Scale (SAS)[1]		X	X	X	X	X	X	X	X	X	X	
Pittsburg Sleep Quality Index (PSQI)		X			X		X			X	X	X
Cogstate Cognition Battery (CBB)												
Cogstate Schizophrenia Battery (CSB)							X				X	
USPA-B	X						X				X	

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; β-hCG = human chorionic gonadotropin; BNSS = Brief Negative Symptoms Scale; CGI-S = Clinical Global Impression – Severity; CBB = Cogstate Brief Battery; CSB = CogState Schizophrenia Battery; C-SSRS = Columbia Suicide Severity Rating Scale ; ECG = Electrocardiogram; ET = early termination; MADRS = Asberg Depression Rating Scale; SAS = Simpson-Angus Scale; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; PSQI = Pittsburg Sleep Quality Index;

[a] Results of assessments from Visit 7 (Week 4) of Study SEP361-201 will serve as Baseline assessments for the present study. NOTE: Subjects may be hospitalized for the first week of the present study if deemed appropriate by the Investigator.

[b] If a subject discontinues from the study, all Visit 11E procedures should be performed at the discontinuation visit, within 48 hours of last study dose.
[c] All subjects will have a safety follow-up visit 7 (± 2) days after their last dose of study drug.
[d] All study drug will be taken once daily in the evening by mouth.
[e] Telephone calls will be made by a member of the research staff to the subjects between scheduled study visits (between Weeks 1 and 2, and at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25) to monitor clinical symptoms and adverse events. If subject appears to be symptomatic, an unscheduled visit will be made as early as possible.
[f] Procedures and assessments for unscheduled visit are: drug accountability, physical and neurological examination, vital signs, ECG, clinical laboratory tests, urine drug screen, PANSS, CGI-S, MADRS, BNSS, AIMS, BARS, SAS, and C-SSRS.
[g] Vital signs will include supine and standing measurements of blood pressure and heart rate and respiratory rate and temperature.
[h] Clinical laboratory tests include: hematology, serum chemistry, urinalysis, serum prolactin, glycosylated hemoglobin (HbA_{1c}), and glucose and lipid panel (subjects must be fasted [no food or drink except water at least 8 hours] prior to collection of blood samples for glucose and lipid panel).
[i] Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected at Visit 2E, 5E, 8E, and 11E (time and date of the 3 previous doses of study medication and the time of the blood sampling must be recorded). Time of food intake relative to study drug taken should be recorded.
[j] Urine drug screen may be ordered at other visits as deemed clinically appropriate. These results should be discussed with the Medical Monitor.
[k] Any positive urine β-hCG test should be confirmed by a serum β-hCG test.
[l] Unscheduled BARS, AIMS, and SAS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment. See Section 10.3.
[m] Titration up to 75 mg/day is permitted (but not required) on Day 4 for reasons of efficacy as an unscheduled visit. At the minimum Investigator will assess AEs, concomitant medications and perform drug accountability at Day 4 unscheduled visit, all other assessments are not required but permitted based on Investigators judgment.
Note: With the exception of the DEQ and the USPA-B, all rating assessments will be performed by the rater using a tablet. In the event that a tablet is not available, the rating assessments will be performed by the rater using a paper version of the assessment.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: List of Abbreviations

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

Table 3: List of Abbreviations (Continued)

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

Table 3: List of Abbreviations (Continued)

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

Table 4: Definition of Key Study Terms

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

4. INTRODUCTION

4.1. Background

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

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

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

4.2. Study Conduct Rationale

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

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

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

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

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

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

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

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

This is an open-label extension study to further evaluate the safety and tolerability of flexibly-dosed SEP-363856 (25, 50 or 75 mg) over 26 weeks of treatment in adult subjects with schizophrenia who completed 4 weeks of double-blind treatment Study SEP361-201.

4.3. Risk-Benefit Assessment

Overall, in previous clinical studies SEP-363856 was generally safe and well tolerated. The pharmacokinetic (PK) and safety profiles observed in adults from completed clinical studies support evaluation of dose levels of 25 to 75 mg/day in adults with schizophrenia.

Schizophrenia is a life-long disorder and despite advances in drug treatment many patients continue to experience symptoms with impaired quality of life. SEP-363856 has a unique mechanism of action and, if successful, could provide a major step forward in the treatment of schizophrenia. Moreover, its unique mechanism of action suggest that it has fewer side effects than traditional antipsychotics and, therefore, is likely to be well tolerated by subjects in this study.

4.4. Hypothesis

This is an open-label extension study to evaluate long-term safety and tolerability of SEP-363856. No statistical hypothesis tests will be performed.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (25, 50, or 75 mg/day [ie, once daily]) in adult subjects with schizophrenia who have completed Study SEP361-201 by the incidence of overall adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation.

5.2. Secondary Objectives

- To evaluate the long-term safety and tolerability of SEP-363856 by assessing vital signs, physical examinations (PE), body weight and body mass index (BMI), 12-lead electrocardiograms (ECG), clinical laboratory evaluations, and suicidal ideation and suicidal behavior using the Columbia - Suicide Severity Rating Scale (C-SSRS)
- To evaluate the long-term effectiveness of SEP-363856 using the Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression-Severity (CGI-S), PANSS subscale scores (positive, negative, general psychopathology), Brief Negative Systems Scale (BNSS), and Montgomery-Asberg Depression Rating Scale (MADRS)
- To explore the long-term maintenance of response in subjects treated with SEP-363856 as measured by the time to relapse and the rate of relapse

5.3. Other Objectives

- To assess whether long-term treatment with SEP-363856 is associated with extrapyramidal symptoms as measured by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS)
- To characterize the long-term effects of SEP-363856 as measured by the Drug Effects Questionnaire (DEQ)
- To characterize the subjective long-term effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI)
- To explore the effects of SEP-363856 on cognition as assessed by the CogState Brief Battery (CBB) and the CogState Schizophrenia Battery (CSB)
- To explore the effects of SEP-363856 on functional outcomes as measured by the UPSA-B total score

6. STUDY ENDPOINTS

6.1. Primary Endpoints

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

6.2. Secondary Endpoints

- Absolute values and changes from double-blind (DB) Baseline of Study SEP361-201 and open-label (OL) Baseline of Study SEP361-202 in clinical laboratory tests (hematology, serum chemistry, urinalysis, glucose and lipid panel, prolactin, glycosylated hemoglobin (HbA_{1c}))
- Absolute values and changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in clinical evaluations (vital signs body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], 12-lead ECGs)
- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS
- Rate of relapse and time to relapse during the 26-week OL period for subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856. Relapse will be defined as the onset of any of the following:
  - An increase in PANSS total score ≥ 30% from the PANSS total score at clinical response and a CGI-S score ≥ 3
  - Re-hospitalization for worsening of psychosis
  - Emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others.
- Changes from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in PANSS total score and subscale scores (positive, negative, and general psychopathology)
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in CGI-S score.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in BNSS total score.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in MADRS total score.
- Proportion of subjects who achieve a response, defined as a 20% or greater improvement in PANSS total score from the baseline, and calculated using (1) the DB Baseline of Study SEP361-201 for subjects assigned to double-blind SEP-363856, and (2) the OL Baseline of Study SEP361-202 for subjects assigned to double-blind placebo.

6.3. Other Endpoints

- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in BARS, AIMS and SAS scores.
- Absolute visual analogue scale (VAS) scores of the DEQ.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in PSQI score.
- Change from DB Baseline of Study SEP361-201 and OL Baseline of Study SEP361-202 in CBB composite score.
- Change from Week 12 of Study SEP361-202 in CSB composite score at Week 26
- Change from OL Baseline of Study SEP361-202 in UPSA-B total score.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 26-week, multiregional, open-label extension study designed to evaluate the long-term safety and tolerability of SEP-363856 for the treatment of subjects with schizophrenia who have completed the 4-week double-blind treatment phase of Study SEP361-201.

Subjects who meet the entry criteria will transition immediately from Study SEP361-201 (at Visit 7; assessments performed at Study SEP361-201 Visit 7 will serve as the Baseline assessments for the present study). Informed consent will be obtained from all subjects before any study procedures are performed for the present study.

Subjects will attend an initial visit on Day 1 (same day as Visit 7 of study SEP361-201). Subjects may be hospitalized for the first week of the present study, if deemed appropriate by the Investigator. During the treatment period, clinic visits will occur as shown in the following figure, during which the procedures outlined in Table 2 will be conducted. Subjects will be seen at weekly intervals for the first 4 weeks, then every 4 weeks thereafter up to week 26. Telephone calls will be made by a member of the clinical research staff to the subjects between scheduled study visits (between Weeks 1 and 2, and at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25) to monitor clinical symptoms and adverse events. If subject appears to be symptomatic, an unscheduled visit will be made as early as possible. Subjects who discontinue early from the study or complete study will be required to complete the follow-up visit 7 days (± 2 days) post last dose of study drug.

Figure 1 Study Schematic

Note: Titration up to 75 mg/day is permitted (but not required) on Day 4 for reasons of efficacy as an unscheduled visit.

All subjects will receive open-label SEP-363856 50 mg/day from Day 1 through Day 3. Beginning on Day 4, flexible dosing ranging from 25 to 75 mg/day is permitted, if deemed clinically necessary (for reasons of safety, tolerability, or efficacy) by the Investigator. On Day 4, subjects are permitted (but not required) to titrate up to 75 mg/day for reasons of efficacy. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visit based on Investigator judgement. Day 4 dosing changes will occur at an unscheduled visit. Thereafter, an increase in dose should occur at weekly intervals in increments of one dose level at a time to a maximum dose of 75 mg/day. Dose reduction for tolerability purposes is allowed at any time during the study.

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

Effectiveness will be evaluated using the PANSS total and subscale scores, as well as CGI-S, BNSS, and MADRS scores.

Subjects will provide information on subjective drug effects via administration of the DEQ. In addition, effects on movement disorders will be measured using the AIMS, BARS and SAS scales. Subjective effects on sleep will be measured by the PSQI scale. Effects on cognition will be assessed by CogState Brief Battery (CBB) and the CogState Schizophrenia Battery (CSB), and a functional outcome measure (UPSA-B total score).

Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected at Visit 2E, 5E, 8E, and 11E. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately.

Subjects who meet any discontinuation/withdrawal criteria will be terminated from the study. Upon termination from the study, hospitalization will be allowed for up to 7 days to stabilize the subject, if necessary. Prior authorization for hospitalization must be approved by the Medical Monitor.

7.2. Treatment Assignment and Blinding

This is an open-label study. All subjects will receive flexible dosing with SEP-363856 (25, 50, or 75 mg/day).

7.2.1. 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 (25, 50 or 75 mg) over 26 weeks of treatment in adult subjects with schizophrenia who completed 4 weeks of double-blind treatment in Study SEP361-201. Long-term effectiveness of SEP-363856 will also be evaluated.

7.3.2. Rationale for the Dosages

In the present study, dosing of SEP-363856 at 25, 50, or 75 mg/day for 26 weeks will be utilized based on observed safety and tolerability in previous studies. Dosages of 50 or 75 mg/day were evaluated in Study SEP361-201. Selection of this dose range was guided by the maximum tolerated dose (MTD) determined for single doses of SEP-363856 administered to healthy adult subjects in Study SEP361-101 (50 mg); the MTD determined for single doses administered to adult subjects with schizophrenia in Study SEP361-105 (75 mg); by the single doses administered to healthy adult subjects (Studies SEP361-103 and SEP361-104 [50 mg]) which

were found to have robust CNS activity). Study SEP361-108 in narcolepsy subjects also demonstrated CNS activity (i.e., REM suppression) at 25 and 50 mg. In addition, dose selection is supported by acceptable safety and tolerability data from the 7-day (10 – 75 mg) and open label 28-day (75 mg) MAD study (Study SEP361-106, Parts 1 and 2) in adult subjects with schizophrenia.

7.4. Prevention of Missing Data

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

- allowance of a dose reduction (from 75 to 50 mg/day or from 50 to 25 mg/day) for drug tolerability purposes
- allowance of some concomitant psychotropic medications during study participation
- train the study centers on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial
- monitor data collection for adherence during the study

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

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Subject must give written informed consent and privacy authorization prior to participation in the study and 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 Study SEP361-201 through Week 4.
3. Subject has not taken any medication other than the study drug for the purpose of controlling schizophrenia symptoms during Study SEP361-201.
4. Female subject must have a negative urine pregnancy test at Visit 7 of Study SEP361-201; females who are post-menopausal (defined as at least 12 months of spontaneous amenorrhea) and those who have undergone hysterectomy or bilateral oophorectomy will be exempted from the pregnancy test. Female subject of reproductive potential agrees to remain abstinent or use highly effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken (See Section 21 Appendix II Highly Effective Contraceptive procedures). In the Investigator's judgment, the subject will adhere to this requirement.
5. Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use highly effective methods of birth control from screening until at least 30 days after the last study drug administration.

8.2. Subject Exclusion Criteria

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

1. Subject answers "yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Visit 7 of Study SEP361-201. Subjects who answer "yes" to this question must be referred to the Investigator for follow-up evaluation.
2. Subject has a clinically significant abnormality including physical examination, vital signs, ECG, or laboratory test at Visit 7 of Study SEP361-201 that the investigator in consultation with the medical monitor considers to be inappropriate to allow participation in the study.
3. Subject has a positive urine drug screen (UDS) or breath alcohol test at Visit 7 of Study SEP361-201.
4. 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	Capsule	Capsule	Capsule
Unit dose	25 mg	50 mg	75 mg
Route of administration	Oral	Oral	Oral
Physical description	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule
Excipients	None	None	None

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in one-week blister cards containing 9 SEP-363856 25 mg, 50 mg, or 75 mg capsules (7 days + 2 extra days).

9.2.2. Labeling Description

All packaging for the study drugs will be labeled with:

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

9.3. Study Drug Storage

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

9.4. Dispensing of Study Drug

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

Study drug blister cards will be assigned by the IXRS based on the treatment schedule and dose adjustment criteria. The IXRS will generate instructions for which medication number to assign to a subject. Each subject will be dispensed one or four 9-day blister cards per scheduled visit depending on the timing of the next scheduled visit (see Table 2).

Subjects will take one capsule of study drug per day at approximately the same time each evening before bed-time. Study drug may be taken with or without food.

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

9.5. Study Drug Accountability

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

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

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

9.6. Study Drug Handling and Disposal

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

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

10. TREATMENT OF SUBJECTS

10.1. Study Drug

All study drug doses will consist of capsule(s) containing SEP-363856 administered orally.

Subjects may take study drug with or without food at approximately the same time each evening before bed-time.

Time and date of food intake must be recorded on Day 8, Day 29, Day 113, and Day 183 when blood samples are collected for determination of SEP-363856 and SEP-363854 concentrations.

10.1.1. Dosage Adjustment Criteria

All subjects will receive open-label SEP-363856 50 mg/day from Day 1 through Day 3. Beginning on Day 4, flexible dosing ranging from 25 – 75 mg/day is permitted, if deemed clinically necessary (for reasons of safety, tolerability, or efficacy) by the Investigator. On Day 4, subjects are permitted (but not required) to titrate up to 75 mg/day. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits based on Investigator judgement. Day 4 dosing changes will occur at an unscheduled visit. Thereafter, an increase in dose should occur at weekly intervals and in increments of one dose level at a time to a maximum dose of 75 mg/day. Dose reduction for tolerability purposes is allowed at any time during the study.

10.2. Treatment Compliance

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

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

10.3. Concomitant Medications and Restrictions

The following information on all medication administered between Visit 1E and Visit 11E or at discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

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

Table 6: Concomitant Medications/Therapies: Use During Study

Type of Drug	Baseline to End of Treatment
Antipsychotic drugs other than study drug	Not Permitted
Mood stabilizers, antidepressants, or antiepileptic drugs	Not Permitted
Fluoxetine or MAO inhibitors	Not Permitted
Clozapine	Not Permitted
Investigational products for other clinical or post-marketing studies	Not Permitted
Electroconvulsive therapy	Not Permitted
Antiparkinsonian drugs	Permitted[a]
Anti-anxiety and Sedative Hypnotic agents	Permitted[a]
Drugs for acute or mild, chronic medical conditions	Permitted[a]
Non-prescription pain medications	Permitted
Herbal supplements (for psychotropic reasons)	Not Permitted

Abbreviations: MAO = Monoamine oxidase.
[a] Permitted doses of these medications are specified in Section 10.3.1 and Section 10.3.2.

10.3.1. Concomitant Nonpsychotropic Medications

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

10.3.2. Concomitant Psychotropic Medications

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

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

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

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

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

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

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

10.3.3. Prohibited Medications

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

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

10.3.4. Prohibited Therapies

Subjects must not receive electroconvulsive therapy (ECT) during the study.

10.4. Other Restrictions

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

10.5. Description of Study Periods and Hospital Discharge

10.5.1. Description of Study Periods

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

Table 7: Description of Study Periods

Study Period	Visit Number	Study Week / Day	Inpatient/Outpatient
Baseline	Visit 1E	Day 1	Inpatient optional (Investigator discretion)
Open Label Treatment Period	Visit 2E	Week 1 / Day 8 ± 2	Outpatient
	Visit 3E	Week 2 / Day 15 ± 2	Outpatient
	Visit 4E	Week 3 / Day 22 ± 2	Outpatient
	Visit 5E	Week 4 / Day 29 ± 3	Outpatient
	Visit 6E	Week 8 / Day 57 ± 3	Outpatient
	Visit 7E	Week 12 / Day 85 ± 3	Outpatient
	Visit 8E	Week 16 / Day 113 ± 3	Outpatient
	Visit 9E	Week 20 / Day 141 ± 3	Outpatient
	Visit 10E	Week 24 / Day 169 ± 3	Outpatient
	Visit 11E	Week 26 / Day 183 ± 3	Outpatient
Follow-up (End of Study)	Visit 12E	Week 27 / Day 190 ± 2 7 days after last dose (subjects who complete or discontinue)	Inpatient optional (Investigator discretion)

10.5.2. Hospital Discharge During the Study

To facilitate enrollment and to optimize treatment compliance, an optional inpatient hospitalization period, at the Investigator's discretion, can occur during the first week of open-label treatment. Subjects are eligible for hospital discharge if they meet all of the following criteria:

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

4. An outpatient environment is available that ensures continued safety for the subject and continued contact with the treatment team for the remainder of the protocol.
5. A reliable informant (family member or caregiver) agrees to confirm adherence to study drug during outpatient study participation.

If the subject cannot be transitioned to an outpatient setting, they must be discontinued from the study. After completion of the follow-up visit or upon study discontinuation; all subjects will be referred for appropriate continued treatment and follow-up care as determined by the Investigator.

10.6. Guidance for Overdose

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

11. STUDY ASSESSMENTS

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

11.1. Demographics and Baseline Characteristics

Demographics (date of birth, sex, ethnicity, race), height, and medical and psychiatric history collected at Visit 1 of Study SEP361-201 will be carried over. Prior and current medications in Study SEP361-201will be carried over and will also be collected in the present study.

11.2. Prior and Concomitant Medication Review

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

11.3. Efficacy Assessments

11.3.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 scales: the Positive scale assesses hallucinations, delusions, and related symptoms; the Negative scale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology scale addresses other symptoms such as anxiety, somatic concern, and disorientation. An anchored Likert scale from 1 - 7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item. Individual items are then summed to determine scores for the 3 scales, as well as a total score. A Composite scale score (Positive scale score minus Negative scale score) can also be calculated to show the relative valence of positive and negative symptoms. Total time required for the PANSS interview and scoring is approximately 30 – 40 minutes (Guy-1976, Kay-1994; Opler-1992; Perkins-2000). PANSS raters will be required to meet specific training and education criteria before they are certified to rate for this study. In addition, raters will receive specific training and education regarding all of the assessments prior to study initiation.

11.3.2. Brief Negative Symptom Scale (BNSS)

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

training and education criteria before they are certified to rate for this study. In addition, raters will receive specific training and education regarding all of the assessments prior to study initiation.

11.3.3. Montgomery-Asberg Depression Rating Scale (MADRS)

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

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

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

11.3.5. CogState Brief Battery (CBB) and CogState Schizophrenia Battery (CSB)

The CBB will be completed at Visit 1E (ie, Baseline, which is the same day as Visit 7 of Study SEP361-201). The CBB assesses four domains. The Detection test (Attention Domain) measures speed of performance. The mean of the log10 transformed reaction times for correct responses are utilized to determine the score. Lower scores correspond to better performance. The Identification test (Information Processing Domain also measures speed of performance. The mean of the log10 transformed reaction times for correct responses are utilized to determine the score. Lower scores correspond to better performance. The One Card Learning test (Visual Learning Domain) measures accuracy of performance. Arcsine transformation of the proportion of correct responses are utilized to determine the domain score. Higher scores correspond to better performance. The One-back Memory test (Working Memory Domain) measures Arcsine transformation of the proportion of correct responses is utilized to determine the domain score. Higher scores correspond to better performance.

The CSB will be completed at Visit 7E (Week 12) and Visit 11E (Week 26). The CSB includes the four domains of the CBB and three additional domains. The Internal Shopping List (Verbal Learning Domain) measures the total number of correct responses made in remembering the list on three consecutive learning trials. Higher scores correspond to better performance. Groton Maze Learning (Problem Solving Domain) measures the total number of errors made in attempting to learn the same hidden pathway on five consecutive trials. Lower scores correspond to better performance. Social Emotional Cognition (Social Cognition Domain) measures accuracy of performance. Arcsine transformation of the proportion of correct responses is utilized to determine the domain score. Higher scores correspond to better performance.

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

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

11.4. Safety Assessments

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

11.4.1. Adverse Events

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

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

11.4.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 22, Appendix III.

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

Any POC (point of care) kits that are performed on site by study personnel rather than in a lab- must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.4.3. Vital Signs

Blood pressure and heart rate measurements will be taken in a sitting and standing position. Respiratory rate and temperature will also be measured and all measurements will be recorded in the eCRF. Clinically significant changes from the signing of the ICF should be captured as AEs in the eCRF.

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

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

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

11.4.4. Electrocardiograms (ECGs)

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

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

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

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

11.4.5. Physical and Neurological Examination

Full PE as well as a neurological examination will be performed. The PE includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

The physical and neurological examination results at Visit 1 (screening) of Study SEP361-201 will be carried over. All PE and neurological exam findings at screening of Study SEP361-201 will be captured in the medical history in the CRF. Any clinically significant changes from screening in Study SEP361-201, as determined by the Investigator, will be noted as AEs in the CRF.

11.4.6. Height, Weight, and BMI

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

Height in meters will be carried over from study SEP361-201. Height will be measured without shoes.

BMI for all visits will be derived within the Electronic Data Capture (EDC) system.

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

11.4.7. Safety Scales

11.4.7.1. Abnormal Involuntary Movement Scale (AIMS)

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

11.4.7.2. Barnes Akathisia Rating Scale (BARS)

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

11.4.7.3. Simpson-Angus Scale (SAS)

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

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

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

11.4.7.5. Drug Effects Questionnaire (DEQ)

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

11.4.7.6. Pittsburg Sleep Quality Index (PSQI)

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

11.5. Population Pharmacokinetic Assessments

All blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be obtained at the same time that other blood samples are taken whenever possible. The time and date of the 3 previous doses of study drug, date, and clock time of blood sampling must be recorded. Date and clock time of food intake must be recorded at Visit 2E, 4E, 8E, and 11E when blood samples are collected for determination of plasma SEP-363856 and SEP-363854 concentrations. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SEP-363856 exposure will be explored using population PK/pharmacodynamics (PD) methods, and reported separately. The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on SEP-363856 plasma exposure will be explored and reported separately. See Section 23 Appendix IV for details including instructions of processing PK samples.

11.6. Study Visits and Assessments

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

11.6.1. Baseline: Visit 1E (Day 1)

Visit 1E of the present study is on the same day as Visit 7 of Study SEP361-201. Subjects will be evaluated at the Open-label Baseline Visit to determine their eligibility for the study. The following procedures will be conducted during this visit:

- Obtain signed informed consent and privacy authorization from the subject before conducting any other visit procedures.
- Inclusion and exclusion criteria
- USPA-B
- Dispense study drug

Results for the following study-related procedures will be carried over from the core study Week 4 visit and do not need to be performed for the Open-label Baseline visit:

- Adverse events monitoring
- Prior/concomitant medication review
- Physical and neurological examinations
- Vital signs
- Weight and waist circumference

- ECG
- Clinical laboratory tests (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel and lipid panel)
- Blood sample for plasma SEP-363856 and SEP-363854
- Urine sample for urinalysis, urine drug screen (UDS), and urine pregnancy test (human chorionic gondadotropin [β-HcG])
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI
- DEQ
- CBB

Procedures are to be completed in the following order:

1. PANSS (study center rater)
2. BNSS (study center rater)
3. MADRS (study center rater)
4. C-SSRS (study center rater)
5. CGI-S (study center rater)
6. AIMS/BARS/SAS
7. PSQI
8. DEQ
9. CSB
10. USPA-B

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

Data such as demographics and height will be carried over from the Screening visit in Study SEP361-201.

Further information on data carried over from Study SEP361-201 will be addressed in the Data Management Plan (DMP).

11.6.2. Visit 2E (Week 1; Day 8 ± 2)

The following procedures will be conducted during this visit:

- Dispense study drug
- Study drug accountability
- AE monitoring
- Prior/concomitant medications.
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel and lipid panel).
- Blood sample for plasma SEP-363856 and SEP-363854
- Urine sample for urinalysis, UDS, and β-hcG (for female subjects).
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI

A telephone contact will be made by a member of the research staff to the subject between Week 1 and Week 2 to monitor clinical symptoms and adverse events. If subject appears to be symptomatic during the telephone contact, an unscheduled visit will be made as early as possible (see Section 11.6.11).

11.6.3. Visit 3E (Week 2; Day 15 ± 2)

The following procedures will be conducted during this visit:

- Dispense study drug
- Study drug accountability
- AE monitoring
- Prior/concomitant medications

- Urine sample for β-hcG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS

11.6.4. Visit 4E (Week 3; Day 22 ± 2)

The following procedures will be conducted during this visit:

- Dispense study drug
- Study drug accountability
- AE monitoring
- Prior/concomitant medications
- Vital sign measurements
- Weight and waist circumference
- Urine sample for β-hcG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS

11.6.5. Visit 5E (Week 4; Day 29 ± 3)

The following procedures will be conducted during these visits:

- Dispense study drug
- Study drug accountability
- AE monitoring

- Prior/concomitant medications
- Physical and neurological examinations
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel and lipid panel)
- Blood sample for plasma SEP-363856 and SEP-363854
- Urine sample for urinalysis, UDS, and β-hcG (for female subjects).
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI

A telephone contact will be made by a member of the research staff to the subject at Weeks 5 and Week 7 to monitor clinical symptoms and adverse events. If subject appears to be symptomatic during the telephone contact, an unscheduled visit will be made as early as possible (see Section 11.6.11).

11.6.6. Visit 6E (Week 8; Day 57 ± 3) and Visit 7E (Week 12; Day 85 ± 3)

The following procedures will be conducted during these visits:

- Dispense study drug
- Study drug accountability
- AE monitoring
- Prior/concomitant medications
- Physical and neurological examinations: Week 8 (Day 57) only
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG

- Urine sample for β-hcG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI: Week 12 (Day 85) only
- CSB: Week 12 (Day 85) only
- USPA-B: Week 12 (Day 85) only

A telephone contact will be made by a member of the research staff at Weeks 9, 11, 13, and 15 to monitor clinical symptoms and adverse events. If subject appears to be symptomatic during the telephone contact, an unscheduled visit will be made as early as possible (see Section 11.6.11).

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

The following procedures will be conducted during these visits:

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

- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS

A telephone contact will be made by a member of the research staff at Weeks 17 and 19. If subject appears to be symptomatic during the telephone contact, an unscheduled visit will be made as early as possible (see Section 11.6.11).

11.6.8. Visit 9E (Week 20; Day 141 ± 3) and Visit 10E (Week 24; Day 169 ± 3)

The following procedures will be conducted during these visits:

- Dispense study drug
- Study drug accountability
- AE monitoring
- Prior/concomitant medications
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG
- Urine sample for β-hcG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI: Week 24 (Day 169) only

A telephone contact will be made by a member of the research staff at Weeks 21, 23, and 25 to monitor clinical symptoms and adverse events. If subject appears to be symptomatic during the telephone contact, an unscheduled visit will be made as early as possible (see Section 11.6.11).

11.6.9. Visit 11E (Week 26; Day 183 ± 3, Early Termination)

The following procedures will be conducted during this visit:

- Study drug accountability
- AE monitoring
- Prior/concomitant medications
- Physical and neurological examination
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel and lipid panel)
- Blood sample for plasma SEP-363856 and SEP-363854
- Urine sample for urinalysis, UDS, and β hcG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI
- DEQ
- CSB
- USPA-B

11.6.10. Visit 12E (Week 27; Day 190 ± 2, Follow-up, End of Study)

All subjects will have a follow-up prior to discharge (7 ± 2 days) after their last dose of study drug. The following procedures will be conducted during this visit:

- AE monitoring
- Prior/concomitant medications.
- Vital sign measurements (prior to ECG)

- Urine sample for β-hcG (for female subjects)
- C-SSRS
- DEQ
- PSQI

11.6.11. Unscheduled Visit (Subjects Who Appear Symptomatic during Telephone Contacts)

If subject appears to be symptomatic during a telephone contact, an unscheduled visit will be made as early as possible. The following procedures will be conducted during this visit:

- Study drug accountability
- AE monitoring
- Prior/concomitant medications
- Physical and neurological examination
- Vital sign measurements (prior to ECG)
- Perform standard 12-lead ECG
- Physical and neurological examination
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel and lipid panel)
- Urine sample for urinalysis, UDS, and β hcG (for female subjects)
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS

If a subject titrates up to 75 mg/day on Day 4 (permitted but not required) an unscheduled visit must occur. The following procedures will be conducted during this visit:

- Study drug accountability
- AE monitoring
- Prior/concomitant medications

Other assessments are not required on Day 4, but are permitted, based on Investigators 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 after first administration of study drug to the last study visit.

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

12.1.2. Serious Adverse Events

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

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

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

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

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

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

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

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

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

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

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

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

12.3. Collection and Recording of Adverse Events

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

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

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

The severity of AE:

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

The frequency of AE:

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

The action taken with the study treatment:

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

The outcome of the AE:

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

The causal relationship of the AE to the study treatment:

- **Not related**

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

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

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

12.4. Immediately Reportable Events

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

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

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

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

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

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

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

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

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

12.4.2. Pregnancy

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

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

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

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

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

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

13.1. Criteria for Subject Termination/Study Drug Discontinuation

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

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

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

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

13.2. Clinical Assessments after Study Drug Discontinuation

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

For subjects who have received study drug and prematurely discontinue from the study treatment (i.e., do not complete through Visit 11E), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.6.9.

All subjects who discontinue from the study early will complete a follow up visit 7 (±2) days after the last visit to assess any post study discontinuation adverse effects as described in Section 11.6.10.

14. STUDY TERMINATION

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

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

In the event of study or site termination, subjects will undergo final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.6.9 and safety follow-up visit as described in Section 11.6.10.

15. STATISTICS

15.1. Sample Size

All subjects who complete the 4-week double-blind treatment period of Study SEP361-201 are eligible. It is anticipated that approximately 180 subjects will enter this open-label extension study.

15.2. Analysis Population

15.2.1. Safety Population

The safety population will consist of all subjects who receive at least one dose of study drug during the 26-week open-label extension period. The safety population will be used for the long-term safety, tolerability, and efficacy analyses.

15.3. Data Analysis

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 extension study treatment, and completed or discontinued the study (including reasons for discontinuation).

15.3.2. Drug Exposure and Compliance

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

Exposure (in days) will be calculated as: last extension study dose date - first extension study dose date + 1. Exposure will be summarized both as a continuous variable (i.e. mean days) and categorically:

- Number and percentage of subjects with extension study drug exposure ≥ 1, ≥ 7, ≥ 14, ≥ 28, ≥ 56, ≥ 84, ≥ 112, ≥ 140, ≥ 168, and ≥ 182 days;
- Number and percentage of subjects with extension study drug exposure for 1 - 6, 7 - 13, 14 - 27, 28 - 55, 56 - 83, 84 - 111, 112 - 139, 140 - 167, 168 - 181, and ≥ 182 days

Percent compliance will be calculated as: (number of capsules taken / number of capsules should have been taken) × 100%. Percent compliance will be calculated by visit and overall for the entire open-label extension period, and will be summarized both as a continuous variable (ie, mean percentage) and categorically (i.e. number and percentage of subjects in each compliance category: non-compliant < 75%, 75% - 125%, non-compliant > 125%, and missing compliance).

Mean daily dose will be calculated for the entire open-label extension 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 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 a review of potentially IPDs. The potentially IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria for the open-label extension study.
- Received any disallowed concomitant medication during the open-label extension period.

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

15.3.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized for the safety population. Selected data (e.g. PANSS total score, CGI-S score, etc.) will be summarized at both the double-blind (DB) baseline of study SEP361-201 and the open-label (OL) baseline of study SEP361-202.

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

15.3.5. Efficacy Analyses

Efficacy data will be summarized descriptively for the safety population.

The absolute values of PANSS total score and subscale scores (positive, negative, and general psychopathology), CGI-S score, BNSS total score, and MADRS total score at both the DB baseline of study SEP361-201 and OL baseline of study SEP361-202, and at each scheduled post-baseline extension visit, will be summarized descriptively.

Changes from baseline in the above efficacy measures will be summarized at each scheduled post-baseline extension visit, based on both the DB baseline of study SEP361-201 and the OL baseline of study SEP361-202.

PANSS total score and CGI-S score data will also be separately summarized by age group, gender, race, and geographic region (i.e. US sites vs. non-US sites). Additional subgroup factors and details of the subgroup analysis will be provided in SAP.

The proportion of subjects who achieve a response, defined as a 20% or greater improvement (i.e. decrease) in PANSS total score from the baseline at the end of the 26-week open-label extension period, will be calculated based on: (1) the DB baseline of study SEP361-201 for subjects assigned to double-blind SEP-363856, and (2) the OL baseline of study SEP361-202 for subjects

assigned to double-blind placebo. For subjects who discontinue early, the PANSS total score measured at the early termination visit will be used.

The CBB composite score at the DB baseline of study SEP361-201 and OL baseline of study SEP361-202 will be calculated. The composite score based on the four domains contained in the CBB scale (i.e. attention, information processing, visual learning, and working memory) will be calculated from the CSB assessment result at Visit 7E (Week 12) and Visit 11E (Week 26) of study SEP361-202. The composite score of CSB at Visits 7E and 11E will also be calculated.

The absolute values of CBB composite score at the DB baseline of study SEP361-201 and the OL baseline of study SEP361-202, and the four-domain composite score at each scheduled post-baseline extension visit, will be summarized descriptively. Changes from baseline in four-domain composite score will be summarized at each scheduled post-baseline extension visit, based on both the DB baseline of study SEP361-201 and the OL baseline of study SEP361-202. In addition, the absolute values of CSB composite score at Visits 7E and 11E of study SEP361-202 will be summarized. Change from Visit 7E in CSB composite score at Visit 11E will also be summarized.

The absolute values of UPSA-B total score at the OL baseline of study SEP361-202, and at each scheduled post-baseline extension visit, will be summarized descriptively. Changes from the OL baseline in UPSA-B total score will be summarized at each scheduled post-baseline extension visit.

15.3.6. Safety Analyses

15.3.6.1. Adverse Events

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

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

For the present study the summary of AEs will be limited to those that occurred on or after the first dose (of the 26-week open-label extension period) of the study drug.

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

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

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

The following conventions will be followed in summarizing AEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.

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

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

15.3.6.2. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables, and by presenting summary statistics for the absolute values as well as the change from Baseline values. Both the DB baseline of study SEP361-201 and the OL baseline of study SEP361-202 will be used in the calculation of change values. For laboratory parameters with categorical outcomes, the number and percentage of subjects with each outcome will be presented. The data listings will flag values outside the reference range.

15.3.6.3. ECGs

Absolute values and changes from Baseline in ECG parameters will be summarized. In addition, the number and percentage of subjects with elevated QTc intervals (> 450 msec, > 480 msec, and > 500 msec) and changes from baseline in QTc intervals ≥ 30 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 DB baseline of study SEP361-201 and the OL baseline of study SEP361-202 will be used in the calculation of change values.

15.3.6.4. Vital Signs

Vital sign parameters, as well as weight and BMI, will be summarized by presenting summary statistics for the absolute values and the change from Baseline values. Both the DB baseline of study SEP361-201 and the OL baseline of study SEP361-202 will be used in the calculation of change values.

15.3.6.5. Physical/Neurological Examination

All physical and neurological exam findings at the screening visit of study SEP361-201 will be recorded as medical history events. Clinically significant findings at the extension visits will be captured as AEs as appropriate and summarized together with the other AEs.

15.3.6.6. Concomitant Medications

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

Any medications taken during the course of the open-label extension study, with a start date on or after the date of the first dose of extension study drug and on or before the date of the last dose

of extension study drug; or with a start date prior to, and an end date on or after, the date of the first dose of extension study drug, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the date of the first dose of extension study drug will be considered prior medications. Medications that started after the date of the last dose of study drug will not be considered concomitant, but will be considered post-treatment. Prior and Concomitant medications will be summarized for the number and percentage of subjects using each medication and by the drug class and preferred name for the safety population.

15.3.6.7. Suicidality Measure

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

15.3.6.8. Rate of Relapse and Time to Relapse

The relapse will be assessed in subjects who demonstrated clinical response to 4 weeks of treatment with SEP-363856. Clinical response is defined as meeting both of the following criteria:

1) a decrease in PANSS total score of ≥ 20% from baseline, and
2) a CGI-S score ≤ 4.

For subjects assigned to double-blind SEP-363856, clinical response will be evaluated using the Day 29 data of study SEP361-201, against the DB baseline of study SEP361-201. For subjects assigned to double-blind placebo, clinical response will be evaluated using the Day 29 data of study SEP361-202, against the OL baseline of study SEP361-202.

Relapse will be identified programmatically using the pre-defined criteria (Section 6.2) among subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856. The rate of relapse will be calculated as the proportion of subjects with a relapse in the 26-week open-label extension period out of all subjects who demonstrated clinical response, along with the 95% confidence interval. The time-to-relapse will be summarized descriptively and will also be presented by a Kaplan-Meier plot.

15.3.6.9. Movement Disorder Measures

Movement disorder measures include AIMS, BARS, and SAS. The absolute values of AIMS, BARS, and SAS total scores at both the DB baseline of study SEP361-201 and OL baseline of study SEP361-202, and at each scheduled post-baseline extension visit, will be summarized for the safety population. Changes from baseline in these measures will also be summarized for each scheduled post-baseline extension visit, using both the DB baseline of study SEP361-201 and OL baseline of study SEP361-202 to calculate the change values.

15.3.6.10. Drug Effects Questionnaire

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

15.3.6.11. Pittsburgh Sleep Quality Index

Absolute PSQI global score at both the DB baseline of study SEP361-201 and OL baseline of study SEP361-202, and at each scheduled post-baseline extension visit, will be summarized for

the safety population. Change from baseline in PSQI global score will also be summarized for each scheduled post-baseline extension visit, based on both the DB baseline of study SEP361-201 and the OL baseline of study SEP361-202.

15.3.6.12. Subgroup Analysis

Selected safety data will be presented by age group, gender, race, and geographic region/country. Additional subgroup factors and details of subgroup analysis of the safety data will be provided in the SAP.

15.3.7. Pharmacokinetic Analysis

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

15.3.8. Pharmacodynamic Analysis

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

15.3.9. Interim Analysis

No interim analysis is planned.

15.3.10. Treatment of Missing Data

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

In this study, missing data will not be imputed. All analyses will be based on the observed data.

15.3.11. Sensitivity Analyses

No sensitivity analysis will be performed.

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

16.2. Computerized Systems Used for Source Data

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

Protocol Step	**Computerized System Type or Description**
Obtain informed consent	A
Review inclusion/exclusion criteria	A
Demographics	A
Prior/concomitant medication review	A
Dispense study drug	A, E
Study drug accountability	A
Physical examination	A
Vital sign measurements	A
Weight	A
Waist circumference	A
Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B
Serum prolactin	B
Glycosylated hemoglobin (HbA1c)	B
Glucose and Lipid panel	B
Serum human chorionic gonadotropin (β-hCG)	B
Blood sample for SEP-363856 PK	D
Urine drug screen	B
Urine β-hCG (local)	A

Protocol Step	Computerized System Type or Description
Urine drug screen (central)	B
Positive and Negative Syndrome Scale (PANSS) – Total Score	F
Clinical Global Impression – Severity (CGI-S)	F
Montgomery-Asberg Depression Rating Scale (MADRS)	F
Columbia Suicide Severity Rating Scale (C-SSRS)	F
Drug Effects Questionnaire (DEQ)	A
Abnormal Involuntary Movement Scale (AIMS)	F
Barnes Akathisia Rating Scale (BARS)	F
Simpson-Angus Scale (SAS)	F
Brief Negative Symptoms Scale (BNSS)	F
Pittsburg Sleep Quality Index (PSQI)	F
CogState Brief Battery (CBB)	G
CogState Schizophrenia Battery (CSB)	G
USPA-B	A
Adverse events (AE) monitoring	A
Statistical analysis	SAS®, version 9.2 or higher

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

16.3. Study Monitoring

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

16.4. Audits

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

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

regulatory authorities and the IEC. Should the Investigator or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

16.5. Study Documentation

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

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

16.6. Clinical Laboratory Certification and Normal Values

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

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

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

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

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

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

17.2. Institutional Review Board/Independent Ethics Committee

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

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

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

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

17.3. Informed Consent

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

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

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

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

17.4. Subject Privacy

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

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

17.5. Protocol Amendments and Emergency Deviations

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

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

17.6. Records Retention

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

17.7. Inspection of Records

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

17.8. Publication Policy

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

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

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

18. REFERENCES

American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. 4th ed; 2000.

Ascher-Svanum H, Zhu B, Faries DE, Salkever D, Slade EP, Peng X, Conley RR. The cost of relapse and the predictors of relapse in the treatment of schizophrenia. BMC Psychiatry. 2010;10:2-7.

Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-676.

Barnes TRE. The Barnes Akathisia Rating Scale – Revisited. J Psychopharmacology 2003; 17(4): 365-370.

Buysse, Daniel J.; Reynolds, Charles F.; Monk, Timothy H.; Berman, Susan R.; Kupfer, David J. (May 1989). "The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research". Psychiatry Research 28 (2): 193–213. .doi:10.1016/0165-1781(89)90047-4

Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacology. 2004;24:192-208.

Guy W. EDCEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76-338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976:534-537.

Kay SR, Opler LA, Fisbein A. Positive and Negative Syndrome Scale Manual. North Tonawanda, NY: Multi-Health Systems, 1994.

Kapur S, Remington G. Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. Annu Rev Med 2001;52:503-517.

Keefe RSE, Bilder RM, Harvey PD, Davis SM, Palmer BW, Gold JM, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology. 2006;31:2033-2046.

Kim DH, Maneen MJ, Stahl SM. Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. Neurotherapeutics. 2009;6:78-85.

Kirkpatrick B, Strauss GP, Nguyen L, et al. The Brief Negative Symptom Scale: Psychometric Properties. Schizophrenia Bulletin. 2011;37(2):300-305. doi:10.1093/schbul/sbq059.

Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull. 2010;36:94-103.

Kuroki T, Nagao N, Nakahara T. Neuropharmacology of second-generation antipsychotic drugs: a validity of the serotonin-dopamine hypothesis. Prog Brain Res. 2008;172:199-212.

Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(suppl 2):1-56.

Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31-41.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-1223.

Mausbach BT, Harvey PD, Goldman SR, Jeste DV, Patterson TL. Development of a brief scale of everyday functioning in persons with serious mental illness. Schizophr Bull. 2007;33:1364–1372.

Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Philips D, Xu, J, Kalali, AH, Schweizer E, Pikalov A, Loebel A. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo-and olanzapine-controlled study. Am J Psychiatry. 2011;168:957-967.

Minzenberg, et al. Chapter 10: Schizophrenia. In: Hales RE, Yudofsky SC, Gabbard GO, eds. The American Psychiatric Publishing Textbook of Psychiatry. 5th edition. Arlington, VA: American Psychiatric Publishing, Inc; 2008.

Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalization in recent-onset schizophrenia. BMC Psychiatry. 2008;8:32-37.

Munetz MR, Benjamin S. How to examine subjects using the Abnormal Involuntary Movement Scale. Hospital and Community Psychiatry 1988; 39: 1172-1177.

Munro J, Osborne S, Dearden L, Pascoe K, Gauthier A, Price M. Hospital treatment and management in relapse of schizophrenia in the UK: associated costs. The Psychiatrist. 2011;35:95-100.

Naber D, Lambert M. The CATIE and CUtLASS studies in schizophrenia: results and implications for clinicians. CNS Drugs. 2009;23:649-659.

Nakamura M, Ogasa M, Guarino J, Phillips D, Severs J, Cucchiaro J, Loebel A. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70:829-836.

Narrow WE, Rae DS, Robins LN, Regier DA. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry. 2002;59:115-123.

National Institute of Mental Health (NIMH). Schizophrenia. http://www.nimh.nih.gov/health/publications/schizophrenia/schizophrenia-booket-2009.pdf. Accessed October 20, 2010.

Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry. 2007;68 (suppl 4):8-13.

Opler LA, Kay SSR, Lindenmayer JP, Fiszbein A. Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS). Toronto: Multi-Health Systems, 1992.

Patel KH, Hlavinka PF. Schizophrenia: Optimal therapy with second-generation antipsychotic agents. Pharmacy Today. 2007;13:71-84.

Pearlson GD. Neurobiology of schizophrenia. Ann Neurol. 2000;48:556-566.

Perkins DO, Stroup TS, Lieberman JA. Psychotic disorders measures. In Handbook of Psychiatric Measures. Washington, D.C.: American Psychiatric Association, 2000 p. 485-513.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry.2007 Jul; 164 (7):1035-1043.

Schultz SK, Andreasen NC. Schizophrenia. Lancet. 1999;353:1425-1430.

Siddiqui O, Hung HM, O'Neil R. MMRM versus LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. Journal of Biopharmaceutical Statistics, 2009; 19: 227-246.

Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavia, Suppl 1970; 212S: 11-19.

Tandon R, Belmaker RH, Gattaz WF, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophrenia Res. 2008;100:20-38.

Webber MA, Marder SR. Better pharmacotherapy for schizophrenia: what does the future hold? Current Psychiatry Reports. 2008;10:352-358.

Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). Br J Psych. 2008; 192: 52-58.

Wu EQ, Shi L, Birnbaum H, Hudson T, Kessler R. Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. Psychol Med. 2006;36:1535-1540.

19. INVESTIGATOR APPROVAL

I have read the protocol, SEP361-202, Version 4.00 "A 26-Week Open-label Safety and Tolerability Extension Study of SEP-363856 in Adult Subjects with Schizophrenia", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

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

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

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

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

2. Subject Restrictions and Instructions

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

3. Reporting

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

4. Data Standardization

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

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

For female subjects

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

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

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

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

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

b. Subjects who are of non-reproductive potential, ie, subject who is surgically sterile, has undergone tubal ligation, or is postmenopausal (defined as at least 12 months of spontaneous amenorrhea or between 6 and 12 months of spontaneous amenorrhea with follicle stimulating hormone (FSH) concentrations within postmenopausal range as determined by laboratory analysis based on study SEP361-201) are not required to remain abstinent or use highly effective contraception**.**

For Male Subjects

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

22. APPENDIX III. CLINICAL LABORATORY TESTS

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

Clinical Safety Panel

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

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Creatine phosphokinase (CPK), Glucose, Hemoglobin A1c (HbA_{1c}), Magnesium (Mg), Phosphorus (P), Potassium (K), Prolactin, Protein (Total), Sodium (Na), Uric Acid

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

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

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

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

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

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

23. APPENDIX IV. PHARMACOKINETIC SAMPLING AND SAMPLE HANDLING GUIDELINE

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

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

For each defined PK sampling time point, collect 6 mL blood sample into a K2-EDTA treated tube. Invert gently 8 to 10 times. Keep the blood collection tube on wet ice, and centrifuge for 20 minutes at ca. x 1300 g to isolate plasma within 30 minutes of blood draw. To ensure a more homogenous sample, all plasma samples should first be transferred to 1 tube, capped and mixed well. Split the harvest plasma sample with approximately equal volume into 2 polypropylene tubes, and label as Primary and Back-up. Freeze plasma tubes in a freezer 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**
Visit 2E (Day 8)	Post-dose (Actual date and time will be recorded)	6 mL
Visit 5E (Day 29)	Post-dose (Actual date and time will be recorded)	6 mL
Visit 8E (Day 113)	Post-dose (Actual date and time will be recorded)	6 mL
Visit 11E (Day 183)	Post-dose (Actual date and time will be recorded)	6 mL