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SEP-363856

Clinical Study Protocol SEP361-118

An Open-Label Positron Emission Tomography Study to Investigate the Effect of Adjunctive Administration of SEP-363856 on Brain Dopamine Synthesis Capacity Using ^{18}F-DOPA in Adult Subjects With Schizophrenia

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

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1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: SEP-363856

Title of Study: An Open-Label Positron Emission Tomography Study to Investigate the Effect of Adjunctive Administration of SEP-363856 on Brain Dopamine Synthesis Capacity Using ^{18}F-DOPA in Adult Subjects with Schizophrenia

Proposed Indication: Schizophrenia

Study Centers: A single center in the United Kingdom (UK)

Phase of Development: 1

Study Objectives:

Primary: To investigate the effect of open-label administration of SEP-363856 (50 or 75 mg/day) adjunctive to an antipsychotic, on brain dopamine synthesis capacity in adults with schizophrenia, as measured by ^{18}F-DOPA positron emission tomography (PET) imaging.

Safety Objective:

- To evaluate the safety and tolerability of adjunctive administration with SEP-363856 (50 or 75 mg/day) in adult subjects with schizophrenia.
- To assess whether adjunctive administration of 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).

Other Objectives:

- To characterize the relationship between brain dopamine synthesis capacity and plasma SEP-363856 and its N-desmethyl metabolite, SEP-363854 exposure.
- To explore the effect of SEP-363856 on resting state functional magnetic resonance imaging (fMRI) as a biomarker of effects in circuits relevant to schizophrenia and cognitive function.
- To explore the effect of SEP-363856 on neuromelanin and iron content (as well as other potential markers identifiable through MRI) and investigate the relationship of these markers with the ^{18}F-DOPA PET measure of dopamine synthesis capacity.
- To investigate the effect of adjunctive open-label administration of SEP-363856 (50 or 75 mg/day) on psychiatric symptoms in adults with schizophrenia.

Study Design:

This is a single-site, open-label, flexibly dosed study evaluating the effect on brain dopamine synthesis capacity as measured by ^{18}F-DOPA PET imaging of adjunctive open-label administration of SEP-363856 (50 to 75 mg/day) over 2 weeks in adults with schizophrenia.

The study will consist of 3 periods: Screening (up to 49 days), Treatment (2 weeks), and a Follow-up visit as shown in Figure 1.

Prior to each PET scan, there is a period of resting state fMRI collection. Two PET scans will be conducted during the study: 1 PET scan prior to dosing (between Day -44 to Day -2) and 1 PET scan following approximately 14 days of treatment (Day 14).

Safety and tolerability will be monitored throughout the study by physical examination, electrocardiogram [ECGs], vital signs, body weight, BMI, collection of adverse events (AEs), clinical

laboratory parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects who have significant findings for suicidal ideation assessed by the C-SSRS at any time during the study must be referred to the Investigator for follow-up evaluation.

Population pharmacokinetic analyses will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between dopamine synthesis capacity and plasma SEP-363856 exposure using population pharmacokinetic (PK)/pharmacodynamics (PD) methods will be explored. The plasma concentrations of the background antipsychotic medication will be examined based on bioanalytical determination, when available.

Exploratory evaluation of the effects of SEP-363856 on psychiatric symptoms will be based on change from baseline to Week 2 on the PANSS, CGI-S, and BNSS rating scales.

Screening Period (up to 49 days):

Informed consent will be obtained from each subject before any study procedures are performed. No imaging procedures involving ionizing radiation will be performed within 12 hours of written consent. Screening procedures will occur over multiple days. Subjects must be on a stable dose of a single antipsychotic medication, dose within the labeled dose-range, for a minimum of 3 weeks or if above the maximum label dose (country specific) for at least 12 weeks prior to the PET scan at the screening visit, and the dose should remain fixed throughout the study. Subjects who meet entry criteria may be in-clinic for up to 7 days during the screening period, at the Investigator's discretion.

During the screening period, those subjects who are outpatients will report to the imaging center for their PET scan at screening (~2 hours duration) and those subjects who are in-clinic will be transferred to the imaging center accompanied by clinic personnel. The PET scan will be performed prior to dosing (Day -44 to Day -2), with administration of ^{18}F-DOPA occurring at the start of the PET scan session.

The screening MRI must occur prior to the PET scan at screening (Day -44 to Day -2). Prior to the PET scan at screening, a blood sample will be taken to determine antipsychotic plasma concentrations.

Subjects who are not already in-clinic will check into the clinic on Day -2.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator. Subjects who screen fail due to MRI or PET scan at screening or fMRI results may not be re-screened.

Open-Label Treatment Period (2 weeks; Day 1 to Day 14+5 days):

Treatment: At Visit 2 (Day 1), subjects who continue to meet all study inclusion criteria and none of the exclusion criteria (see below) will begin treatment with SEP-363856 as an adjunct to their background, stable antipsychotic treatment. Study drug dosing will begin on Day 1. Study drug (Days 1 – 13) should be taken approximately the same time each day with morning dosing recommended. Doses may be moved to the evening for reasons of tolerability. The final dose, on Day 14, should occur approximately 2 to 4 hours prior to the final PET scan. Treatment with SEP-363856 will occur once-daily during the treatment period with procedures outlined in Table 2 (schedule of assessments). Subjects will receive SEP-363856 50 mg/day on Day 1 through Day 3. On Day 4, subjects will titrate up to a dose of 75 mg/day. A one-time dose reduction (from 75 mg to 50 mg) for tolerability purposes is permitted and may occur at any time, at the Principal Investigator's discretion. Subjects who have a dose reduction for tolerability will continue to receive the reduced dose for the remainder of the study. Subjects will remain in-clinic and on treatment through Week 2 until all Day 14 assessments including the PET scan are complete. In the event of an unsuccessful PET scan on Day 14, additional days of dosing may be necessary up to, but not exceeding, Day 19. If any such additional days are necessary, subjects will remain in the clinic and continue their usual daily dosing. All Day 14 assessments are to be completed the same day as the PET scan. Subjects will be eligible for clinic discharge at the Week 2 visit, at the Investigator's discretion.

Blood samples for determination of SEP-363856 and SEP-363854 plasma concentrations will be collected on Day 1 (predose), Day 2 (postdose), Day 7 (postdose), and Day 14 (prior to PET scan). Blood samples for antipsychotic plasma concentrations will be collected on Day -2, Day 1 (predose), Day 2 (postdose), Day 7 (postdose), and Day 14 (prior to PET scan). Blood samples for SEP-363856, SEP-363854 and antipsychotic plasma concentrations should be collected at approximately the same time as dosing for Day 2 (postdose) and Day 7 (postdose) while the Day 14 collection should occur immediately prior to the PET scan.

Administration of ^{18}F-DOPA will occur at the start of the PET scan session. Clinical assessments as described in the Schedule of Assessments (SOA) will be performed.

Follow-up/End of Study (EOS) (7± 2 days after last day of study drug):

A follow-up visit will occur 7 days (± 2 days) after last day of study drug. Clinical assessments as described in the Schedule of Assessments (SOA) will be performed.

Early Termination:

Subjects who discontinue early from the study will complete an early termination visit. Clinical assessments as described in the Schedule of Assessments (SOA) will be performed.

Number of Subjects (planned): 22 subjects

Diagnosis and Main Criteria for Subject Inclusion:

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

- Male or female subject between 18 to 45 years of age (inclusive) at the time of consent.
- Subject meets Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for a primary diagnosis of schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the Structured Clinical Interview for DSM-V Clinical Trials Version [SCID-CT]). The duration of the subject's illness whether treated or untreated must be ≥ 6 months.
- Subject must be on a stable dose of a single antipsychotic medication, dosed within the labeled dose-range, for a minimum of 3 weeks prior to the PET scan at the screening visit. Patients taking clozapine are not eligible to participate.

Investigational Product, Dosage and Mode of Administration:

SEP-363856 will be supplied as 50 mg or 75 mg tablets administered orally once daily. Study drug (Days 1 – 13) may be taken without regard to food at approximately the same time each day with morning dosing recommended. Doses may be moved to the evening for reasons of tolerability. The final dose, Day 14, should occur approximately 2 to 4 hours prior to the final PET scan.

Duration of Treatment: Once daily open-label treatment for 2 weeks

Reference Therapy, Dosage and Mode of Administration: not applicable

Concomitant Medications:

Following is a summary of allowed/disallowed concomitant medications. Further details are provided in Section 10.3**.**

Concomitant use of CYP2D6 inhibitors is prohibited as SEP-363856 is a potential substrate for CYP2D6.

Caution should be taken with concomitant use of CYP2D6 substrates with SEP-363856 as SEP-363856 is a weak inhibitor of CYP2D6 (see Section 25).

Concomitant Non-psychotropic Medications:

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after enrollment if the dose and regimen have been stable (± 25%) for at least 30 days prior to screening. The concomitant medication dose may change, as needed, after enrollment (or be discontinued). β-adrenergic antagonists used to treat stable hypertension may be continued through the screening phase and post-initiation. 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. Hydrocortisone 1% cream or ointment for treatment of contact dermatitis from ECG pads is allowed. Female subjects may use oral, patch, or intrauterine device (IUD) hormonal contraceptives, or progestin implant or injection (contraception requirements are defined in protocol Section 10.5). Medications for short-term treatment of a medical condition (no more than 10 days) may be allowed with consultation with the Medical Monitor.

Prior Medications:

Subjects must be on a stable dose of a single antipsychotic medication, dose within the labeled dose-range, for a minimum of 3 weeks or if above the maximum label dose (country specific) for at least 12 weeks prior to the PET scan at the screening visit, and the dose should remain fixed throughout the study. Depot neuroleptic dose must be stable for at least 2 treatment cycles or at least 30 days (whichever is longer) prior to the screening visit.

Prior exposure to clozapine is allowed, as long as treatment is discontinued at least 120 days prior to PET scan at screening. All other psychotropic medication (with the exception of the single background antipsychotic, or medications listed below), must be discontinued, as tolerated and clinically appropriate, prior to PET scan at screening in a manner that is consistent with labeling recommendations and conventional medical practice.

Concomitant Psychotropic Medications:

Subjects who require treatment with a prohibited concomitant medication during the treatment period will be discontinued from 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) or procyclidine (up to 30 mg/day). Treatment with propranolol (up to 120 mg/day) will be permitted as needed for akathisia.

Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem, and zolpidem CR (controlled release) 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), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) 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 sedative/hypnotic 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). 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 prohibited concomitant medications (including antidepressants, mood stabilizers, or anxiolytics [lorazepam or equivalent at doses above protocol-specified limits]) will be discontinued (as appropriate) from the study. Continuation of subjects who require an increase in dose of their background antipsychotic during the study will be discussed with the Medical Monitor. A down-titration of the background antipsychotic due to tolerability may be allowable, after consultation with the Medical Monitor. All efforts will be made to complete the PET and resting state fMRI scans intended by the protocol even in cases of discontinuations of study drug or procedures.

Study Endpoints:

Primary Endpoint: Change from baseline in dopamine synthesis capacity at Week 2 using ^{18}F-DOPA.

Safety Endpoints:

- Incidence of treatment emergent adverse events (TEAEs), serious AEs (SAEs), and adverse events (AEs) (or SAEs) leading to discontinuation.
- Absolute values and changes from baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, body mass index [BMI], 12-lead ECG parameters).
- Frequency and severity of suicidal ideation or suicidal behavior as measured by the C-SSRS.
- Change from Baseline in BARS, AIMS, and SAS scores at Week 2 and Week 3.

Other Endpoints:

- Change in baseline resting state BOLD fMRI signal at Week 2.
- Change in exploratory MRI markers, including but not limited to neuromelanin signal as measured by neuromelanin sensitive MRI (NM-MRI) and iron signal as measured by an iron-sensitive MRI sequence (effective transverse relaxation rate [R2*] or Quantitative Susceptibility Mapping [QSM]), at Week 2.
- Plasma concentrations of SEP-363856 and its metabolite SEP-363854 at each postdose timepoint.
- Change from baseline to Week 2 in:
  - Positive and Negative Syndrome Scale (PANSS) score.
  - Brief Negative Symptom Scale (BNSS) Montgomery-Asberg Depression Rating Scale (MADRS) total score.
  - Clinical Global Impression-Severity (CGI-S) score.

Statistical Methods:

PET Analysis: The region of interest in the primary endpoint is the whole striatum. Exploratory analyses will be conducted in other regions and sub-regions of interest. The cerebellum will be used

as the reference region. Dopamine synthesis capacity will be calculated based on each individual PET images collected at each scan for each subject.

Statistical Analysis: The analysis of brain dopamine synthesis capacity and fMRI analysis will use the PET population, which include subjects who were administered at least one dose of SEP-363856 and have a baseline and a post-baseline PET assessment. The change from baseline in dopamine synthesis capacity at Week 2 will be calculated, together with 95% confidence interval from a paired sample t distribution. Changes in resting state BOLD fMRI signal at each post-dose time point from baseline will be summarized. Changes in exploratory MRI markers, including (but not limited to) neuromelanin and iron signal at each post-dose time point from baseline will be summarized. The efficacy population will include all subjects who have received at least one dose of SEP-363856, and have any postdose data for the PANSS, CGI-S, BNSS or MADRS. Efficacy data will be based on this population. Changes from baseline at each post-dose time point will be summarized, with 95% confidence intervals.

Safety analyses will use the Safety population, which includes all subjects who have received at least one dose of study drug. Safety measures will be summarized descriptively.

Treatment emergent adverse events (TEAEs) will be summarized by presenting the number and percentage of subjects with any TEAEs, and AEs by system organ class and preferred term. Adverse events will be further summarized by severity and by relationship to study drug. The summary of TEAEs will be limited to events occurring on or after the first dose of study drug. All AEs, as well as a listing of deaths, SAEs, or AEs leading to discontinuation, will be presented in listings.

Vital signs, ECG parameters, and laboratory data will be summarized by presenting summary statistics of actual values and change from baseline values. The number and percentage of subjects with potentially clinically significant post-baseline values for selected parameters will be presented. The incidence of orthostatic hypotension and orthostatic tachycardia will be summarized.

The BARS, AIMS, and SAS will be summarized descriptively by presenting summary statistics of actual values and change from baseline values.

The relationship between dopamine synthesis capacity at baseline and measures of baseline symptom severity (PANSS, CGI-S, BNSS, and MADRS) and their change from baseline will be presented graphically.

Sample Size: This study is designed to determine the magnitude of a possible pharmacological effect of SEP-363856 on dopamine synthesis capacity. Measurement of dopamine synthesis capacity has shown good test-retest reliability (Egerton-2010). Prior studies have reported a within-subject standard deviation of 0.00056/min in dopamine synthesis capacity. The absolute elevation in dopamine synthesis capacity for schizophrenia cases versus normal healthy controls is estimated to be approximately 0.001/min and to have a correlation of approximately 0.6 with symptoms. Given this relationship between dopamine synthesis capacity and symptoms, it is estimated that a decrease in dopamine synthesis capacity of 0.0005/min in patients is the smallest reduction likely to be clinically significant (anticipated to translate into > 20% reduction in symptoms, which is generally considered the smallest change readily detected in clinical practice). A sample size of 16 subjects treated with SEP-363856 will provide > 90% power to detect a treatment reduction of 0.0005/min (change from baseline) in dopamine synthesis capacity using a paired sample t-test with alpha set at the 0.05 level.

Subjects who are initiated on treatment but discontinue from the study may not be replaced. The total sample size will be 22 subjects to allow for up to 25% drop-out to obtain complete PET scans on at least 16 subjects.

Table 2: Schedule of Assessments

Study Visit Number	**Visit 1**	**Visit 2**				**Visit 3**	**ET**
Study Visit Week	**Screening[a]**	**Check-in**		**Day 1**	**Week 2**	**Week 3 Follow-up/ EOS**	**Early Termination**
Study Visit Type	**Outpatient or In-clinic up to 7 days[b]**	**In-clinic**		**In-clinic**	**In-clinic**	**Outpatient**	**-**
Study Visit Day	**-49 to -2**	**-2**	**-1**	**1**	**14 + 5 days**	**7 ± 2 days post last dose of study drug**	**-**
Obtain informed consent	X						
Review inclusion/exclusion criteria	X	X	X	X			
Demography	X						
Prior/concomitant medication review	X	X	X	X	X	X	X
Dispensation of study drug (blister card)				X[c]			
Administration of Study Drug[c]				X	X		
Admit to Clinic, if not admitted during screening		X[b]					
Clinic Discharge					X		
Medical history	X						
Psychiatric history/mental status	X						
SCID-CT[d]	X						
Physical examination	X					X	X
Height/BMI	X						
Vital signs[e]	X	X	X	X	X	X	X
Weight	X	X		X	X	X	X
Electrocardiogram (ECG)	X	X		X	X	X	X
Hematology, chemistry, and urinalysis	X	X			X	X	X
Coagulation Panel	X						
Thyroid Panel	X						

Table 2: Schedule of Assessments (Continued)

Study Visit Number	Visit 1	Visit 2				Visit 3	ET
Study Visit Week	Screening[a]	Check-in		Day 1	Week 2	Week 3 Follow-up/ EOS	Early Termination
Study Visit Type	Outpatient or In-clinic up to 7 days[b]	In-clinic		In-clinic	In-clinic	Outpatient	-
Study Visit Day	-49 to -2	-2	-1	1	14 + 5 days	7± 2 days post last dose of study drug	-
Serum prolactin	X	X			X	X	X
Hepatitis B/C, HIV-1/HIV-2	X						
Glycosylated hemoglobin (HbA_{1c})	X						
Glucose and lipid panel[f]	X	X			X	X	X
Follicle stimulating hormone (FSH), females only[g]	X						
Serum human chorionic gonadotropin (β-hCG), females only	X						
Urine β-hCG[h], females only	X	X		X (predose)	X	X	X
Blood sample for pharmacogenomics				X			
Blood sample for SEP-363856 and SEP-363854 PK[i]				X	X	X	X
Blood sample for antipsychotic levels[j]	X	X		X	X	X	X
Urine drug screen[k]	X	X		X	X	X	X
Magnetic resonance imaging (MRI) Scan	X						
PET/MR Scan including fMRI[l]	X (Day -44 to -2)				X[m]		X[n]
Positive and Negative Syndrome Scale (PANSS)	X		X[s]		X[m] (±1 day of PET Scan)		X[o]
Brief Negative Symptom Scale (BNSS)	X		X[s]		X[m] (±1 day of PET Scan)		X[o]
Montgomery-Asberg Depression Rating Scale (MADRS)			X[s]		X[m] (±1 day of PET Scan)		X[o]

Table 2: Schedule of Assessments (Continued)

Study Visit Number	**Visit 1**	**Visit 2**				**Visit 3**	**ET**
Study Visit Week	**Screening[a]**	**Check-in**		**Day 1**	**Week 2**	**Week 3 Follow-up/ EOS**	**Early Termination**
Study Visit Type	**Outpatient or In-clinic up to 7 days[b]**	**In-clinic**		**In-clinic**	**In-clinic**	**Outpatient**	**-**
Study Visit Day	**-49 to -2**	**-2**	**-1**	**1**	**14 + 5 days**	**7± 2 days post last dose of study drug**	**-**
Columbia Suicide Severity Rating Scale (C-SSRS)[p]	X		X[s]		X	X	X
Clinical Global Impression – Severity (CGI-S)	X		X[s]		X[m] (±1 day of PET Scan)		X[o]
Barnes Akathisia Rating Scale (BARS)[q]				X (predose)[t]	X	X	X
Abnormal Involuntary Movement Scale (AIMS)[q]				X (predose)[t]	X	X	X
Simpson-Angus Scale (SAS)[q]				X (predose)[t]	X	X	X
Adverse events (AEs) monitoring[r]	X	X	X	X	X	X	X

Abbreviations: BARS = Barnes Akathisia Rating Scale; BMI = body mass index; AIMS = Abnormal Involuntary Movement Scale; SAS = Simpson-Angus Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; EOS = end of study; ET = early termination; fMRI = functional magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; MR = magnetic resonance; SCID-CT = structured clinical interview for DSM-V, clinical trials version.

[a] Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator. Subjects who screen fail due to MRI or PET or fMRI results may not be re-screened. Screening procedures will occur on multiple days. If subject re-screened, an MRI (without any abnormality) obtained at the study's imaging center within 90 days prior to Day -1 check-in is acceptable for eligibility.

[b] Extension of in-clinic stay during the screening phase to complete screening assessments may be allowed on a case-by-case basis with pre-approval of the Medical Monitor. Subject must be admitted to the clinic by Day -2.

[c] Dispensation of study drug on Day 1 and Day 8. All study drug will be taken once daily by mouth from Day 1 through Week 2 (Day 14). After 3 days of treatment with 50 mg/day SEP-363856, subjects are required to titrate up to 75 mg/day. Subjects may dose reduce one time to 50 mg/day for tolerability reasons at any time. Subjects who have a dose reduction for tolerability will continue to receive the reduced dose for the remainder of the study. The final dose, on Day 14, should occur approximately 2 to 4 hours prior to the final PET scan.

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

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

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

[g] Blood samples for follicle stimulating hormone (FSH) will be collected if menopause is suspected.
[h] Any positive urine β-hCG test should be confirmed by a serum β-hCG test. Must be performed prior to PET scan on same day as screening scan and on Day 14 scan.
[i] Blood samples for determination of SEP-363856 and SEP-363854 concentrations will be collected on Day 1 (approximately 10 minutes prior to dosing), Day 2 (2 – 4 hours postdose), Day 7 (2 – 4 hours postdose), Day 14 (prior to PET scan), and at Follow-up.
[j] Blood samples for antipsychotic plasma concentrations will be collected at Screening, Day -2, Day 1 (approximately 10 minutes prior to dosing), Day 2 (2 - 4 hours postdose), Day 7 (2 – 4 hours postdose), Day 14 (prior to PET scan), and at Follow-up.
[k] Additional urine drug screen may be ordered as deemed clinically appropriate. These results should be discussed with the Medical Monitor.
[l] Each PET scan will be accompanied by intravenous administration of radiotracer ^{18}F-DOPA and oral pre-treatment (1 hour prior to tracer) with 150 mg carbidopa and 400 mg entacapone. If PET/MR scanner is unavailable for technical reasons separate PET and MR scans (on an alternate PET scanner without MR and alternate MR scanner) will be permitted. Prior to each PET scan, there is a period of resting state fMRI collection. In addition to fMRI scan sequences, exploratory MRI sequences may be performed during each of the MRI and PET/MR acquisition times and may include (but not limited to) a neuromelanin-sensitive MRI (NM-MRI) sequence and an iron-sensitive MRI sequence (effective transverse relaxation rate [R2*] or Quantitative Susceptibility Mapping [QSM]). Repeat MRI including exploratory MRI sequences may be performed where it is not possible to obtain complete measures during the PET-MRI scan.
[m] In the event of unsuccessful PET scan on Day 14, additional days of dosing may be necessary up to, but not exceeding, Day 19. If any such additional days are necessary, subjects will continue their usual daily dosing. PANSS, BNSS, MADRS, and CGI-S may be assessed ±1 day of PET scan; other assessments are to be completed the same day as the PET scan. Participants will only receive 3 PET scans in the event that a scan is not able to be completed or is not suitable for analysis. It is expected that the majority of participants will receive up to 2 PET scans which would result in an effective dose of 7.4 mSv.
[n] PET scan to be performed at early termination (ET) visit only if the subject terminates the study prior to Day 14 PET scan.
[o] Only perform PANSS, BNSS, CGI-S, and MADRS if subject discontinues prior to Day 14 scan day.
[p] At the screening visit, the “Baseline/Screening” version will be completed; the “Since Last Visit” version of the C-SSRS will be administered for all other visits. C-SSRS should be performed prior to PET scan on Day 14.
[q] Unscheduled BARS, AIMS, and SAS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment.
[r] All adverse events occurring after signing informed consent through the end of study will be collected.
s PANSS, BNSS, MADRS, CGI-S, and C-SSRS to be completed on Day -2 or Day -1.
t BARS, AMES, SAS to be collected on Day -1 or Day 1 (predose).

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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
AST	Aspartate aminotransferase
BARS	Barnes akathisia Rating Scale
BMI	Body mass index
BNSS	Brief Negative Symptom Scale
CDR	Clinical data repository
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
DSM-V, DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ET	Early termination
ePRO	Electronic patient reported outcomes
FDA	U.S. Food and Drug Administration
fMRI	Functional magnetic resonance imaging
GCP	Good Clinical Practice
5-HT	5-hydroxytryptamine (serotonin)

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
HIV	Human immunodeficiency virus
HRA	Health Research Authority
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational product
IPD	Important protocol deviation
IRB	Institutional Review Board
LIMS	Laboratory information management system
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCS	Not clinically significant
PANSS	Positive and Negative Syndrome Scale
PCS	Potentially clinically significant
PET	Positron emission tomography
PK	Pharmacokinetic(s)
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
PVG	Pharmacovigilance
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
RR	RR interval
SAE	Serious adverse event
SAS	Simpson-Angus scale
SCID-CT	Structured clinical interview for DSM, clinical trials version
SOC	System organ class
TEAE	Treatment emergent adverse event
WBC	White blood cells
WHO-DD	World Health Organization – Drug Dictionary

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled/randomized.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and/or active control.
Treatment Period	The period of the study in which the study drug is administered.
Completed Treatment	Any subject who participated throughout the duration of the 14-day treatment period, up to and including the Day 14 PET/fMRI scan.
Completed Study	Any subject who completed treatment and the last planned 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.
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 disordered thought), negative symptoms (eg, flat affect, anhedonia, alogia, and avolition), and cognitive deficits (eg, impaired memory, attention, and planning/organizing). Mood symptoms such as depression, anxiety, hostility, and excitement can also be present in patients with schizophrenia (Patel-2007; 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, and the side effects associated with current treatments. New treatments with greater efficacy and tolerability are needed to reduce the associated high rates of morbidity and mortality (Lehman-2004; Tandon-2008; 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, QT prolongation, extrapyramidal symptoms, and tardive dyskinesia (Davis-2004; Lieberman-2005; Newcomer-2007; Leucht-2009), which may lead to significant comorbid medical problems as well as contribute to poor compliance and treatment discontinuation. The large scale NIMH-CATIE schizophrenia study found that 70% to 80% of outpatients discontinue medications due to lack of efficacy or occurrence of side effects (Lieberman-2005), often leading to relapse of symptoms and the need for rehospitalization (Ascher-Svanum-2010; Munro-2011; Morken-2008). Clearly, an unmet need exists for new, effective, and well-tolerated treatments.

4.2. Study Conduct Rationale

SEP-363856 is currently being investigated in subjects with schizophrenia. One randomized, double-blind study (SEP361-201) evaluating efficacy and safety of flexible SEP-363856 doses (50 mg/day or 75 mg/day) in adult subjects with schizophrenia is complete. Subjects who completed this study were eligible to enroll in a 26-week-long-term open-label safety and tolerability study (SEP361-202).

The primary objective of the current study is to investigate the effect of open-label administration of SEP-363856 (50 or 75 mg/day) adjunctive to an antipsychotic, on brain dopamine synthesis capacity, as measured by ^{18}F-DOPA positron emission tomography (PET) imaging, in adults with schizophrenia.

4.3. Risk-Benefit Assessment

Overall, in previous clinical studies, SEP-363856 was generally well-tolerated. The pharmacokinetic (PK) and safety profiles observed in healthy male subjects and male and female subjects with schizophrenia from completed Phase 1 clinical studies, as well as safety data from the completed Phase 2 double-blind and clinically complete open-label extension study in adults with schizophrenia, support the evaluation of SEP-363856 in the dose range of 50 to 75 mg/day in adults with schizophrenia.

Schizophrenia is a life-long disorder and despite advances in drug treatment many patients continue to experience symptoms with impaired quality of life. SEP-363856 has a novel mechanism of action not related to direct antagonism of the D2 receptor. If proven effective and well-tolerated, it may provide an advance in the treatment of patients with schizophrenia by reducing the side-effect burden associated with direct D2 receptor antagonists.

5. STUDY OBJECTIVES

5.1. Primary Objective

To investigate the effect of open-label administration of SEP-363856 (50 or 75 mg/day) adjunctive to an antipsychotic, on brain dopamine synthesis capacity in adults with schizophrenia, as measured by ^{18}F-DOPA positron emission tomography (PET) imaging.

5.2. Safety Objectives

- To evaluate the safety and tolerability of adjunctive administration with SEP-363856 (50 or 75 mg/day) in adults with schizophrenia.
- To assess whether adjunctive administration of 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).

5.3. Other Objectives

- To characterize the relationship between brain dopamine synthesis capacity and plasma SEP-363856 and its N-desmethyl metabolite, SEP-363854, exposure.
- To explore the effect of SEP-363856 on neuromelanin and iron content (as well as other potential markers identifiable through MRI) and investigate the relationship of these markers with the ^{18}F-DOPA PET measure of dopamine synthesis capacity.
- To explore the effect of SEP-363856 on resting state functional magnetic resonance imaging (fMRI) as a biomarker of effects in circuits relevant to schizophrenia and cognitive function.
- To investigate the effect of adjunctive open-label administration of SEP-363856 (50 or 75 mg/day) on psychiatric symptoms in adults with schizophrenia.

6. STUDY ENDPOINTS

6.1. Primary Endpoint

Change from baseline in dopamine synthesis capacity at Week 2 using ^{18}F-DOPA.

6.2. Safety Endpoints

- Incidence of treatment emergent adverse events (TEAEs), serious AEs (SAEs) and AEs (or SAEs) leading to discontinuation.
- Absolute values and changes from baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, body mass index [BMI], 12-lead electrocardiogram [ECG] parameters).
- Frequency and severity of suicidal ideation or suicidal behavior as measured by the C-SSRS.
- Change from Baseline in BARS, AIMS and SAS scores at Week 2 and Week 3.

6.3. Other Endpoints

- Change in baseline resting state BOLD fMRI signal at Week 2.
- Change in exploratory MRI markers, including but not limited to neuromelanin signal as measured by neuromelanin sensitive MRI (NM-MRI) and iron signal as measured by an iron-sensitive MRI sequence (effective transverse relaxation rate [R2*] or Quantitative Susceptibility Mapping [QSM]), at Week 2.
- Plasma concentrations of SEP-363856 and its metabolite SEP-363854 at each postdose timepoint.
- Change from baseline to Week 2 in:
  - Positive and Negative Syndrome Scale (PANSS) scores.
  - Brief Negative Symptom Scale (BNSS).
  - Montgomery-Asberg Depression Rating Scale (MADRS) total score.
  - Clinical Global Impression-Severity (CGI-S) score.

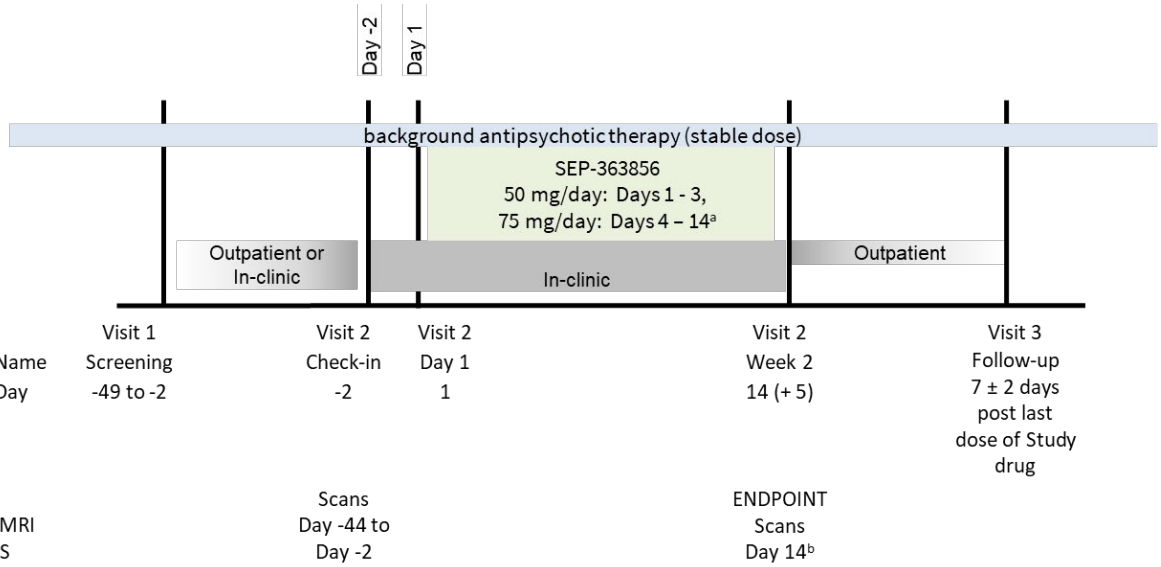
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a single-site, open-label, flexibly dosed study evaluating the effect on brain dopamine synthesis capacity as measured by ^{18}F-DOPA PET imaging of adjunctive open-label administration with SEP-363856 (50 to 75 mg/day) over 2 weeks in adults with schizophrenia.

The study will consist of 3 periods: Screening (up to 49 days), Treatment (2 weeks), and a Follow-up visit as shown in Figure 1.

Figure 1: Study Schematic



[a] Dose reduction to 50 mg/day allowed for reasons of tolerability.
[b] Subject must remain in-clinic and on treatment until completion of the Visit 2 assessments, including scans. In the event of an unsuccessful PET scan on Day 14, additional days of dosing may be necessary up to, but not exceeding, Day 19

Prior to each PET scan, there is a period of resting state fMRI collection. Two PET scans will be conducted during the study: 1 PET scan prior to dosing (between Day -44 to Day -2) and 1 PET scan following approximately 14 days of treatment (Day 14).

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

Population pharmacokinetic analyses will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between dopamine synthesis capacity and plasma SEP-363856 exposure using population

PK/pharmacodynamics (PD) methods will be explored. The plasma concentrations of the background antipsychotic medication will be examined based on bioanalytical determination, when available.

Exploratory evaluation of the effects of SEP-363856 on psychiatric symptoms will be based on change from baseline to Week 2 on the PANSS, CGI-S, and BNSS rating scales.

Screening Period (up to 49 days):

Informed consent will be obtained from each subject before any study procedures are performed. No imaging procedures involving ionizing radiation will be performed within 12 hours of written consent. Screening procedures will occur over multiple days. Subjects must be on a stable dose of a single antipsychotic medication, dose within the labeled dose-range, for a minimum of 3 weeks or if above the maximum label dose (country specific) for at least 12 weeks prior to the PET Scan at the screening visit, and the dose should remain fixed throughout the study. Subjects who meet entry criteria may be in-clinic for up to 7 days during the screening period, at the Investigator's discretion.

During the screening period, those subjects who are outpatient will report to the imaging center for their PET scan at screening (~2 hours duration) and those subjects who are in-clinic will be transferred to the imaging center accompanied by clinic personnel. The PET scan will be performed prior to dosing (Day -44 to Day -2), with administration of ^{18}F-DOPA occurring at the start of the PET scan session.

The screening MRI must occur prior to the PET scan at screening (Day -44 to Day -2). Prior to the PET scan at screening, a blood sample will be taken to determine antipsychotic plasma concentrations.

Subjects will check into the clinic on Day -2.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator. Subjects who screen fail due to MRI or PET or fMRI results may not be re-screened.

Open-Label Treatment Period (2 weeks; Day 1 to Day 14 + 5 days):

Treatment: At Visit 2 (Day 1), subjects who continue to meet all study inclusion criteria and none of the exclusion criteria (see below) will begin treatment with SEP-363856 as an adjunct to their background, stable antipsychotic treatment. Study drug dosing will begin on Day 1. Study drug (Days 1 – 13) should be taken approximately the same time each day with morning dosing recommended. Doses may be moved to the evening for reasons of tolerability. The final dose, on Day 14, should occur approximately 2 to 4 hours prior to the final PET scan. Treatment with SEP-363856 will continue once-daily during the treatment period with procedures outlined in Table 2 (schedule of assessments). Subjects will receive SEP-363856 50 mg/day on Day 1 through Day 3. On Day 4, subjects will titrate up to a dose of 75 mg/day. A one-time dose reduction (from 75 mg to 50 mg) for tolerability purposes is permitted and may occur at any time, at the principal Investigator's discretion. Subjects who have a dose reduction for tolerability will continue to receive the reduced dose for the remainder of the study. Subjects will remain in-clinic and on treatment through Week 2 until all Day 14 assessments including the PET scan are complete. In the event of an unsuccessful PET scan on Day 14, additional days of dosing may be necessary up to, but not exceeding, Day 19. If any such additional days are

necessary, subjects will remain in the clinic and continue their usual daily dosing. All Day 14 assessments are to be completed the same day as the PET scan. Subjects will be eligible for clinic discharge at the Week 2 visit, at the Investigator's discretion.

Blood samples for determination of SEP-363856 and SEP-363854 plasma concentrations will be collected on Day 1 (predose), Day 2 (postdose), Day 7 (postdose), and Day 14 (prior to PET scan). Blood samples for antipsychotic plasma concentrations will be collected on Day -2, Day 1 (predose), Day 2 (postdose), Day 7 (postdose), and Day 14 (prior to PET scan). Blood samples for SEP-363856, SEP-363854 and antipsychotic plasma concentrations should be collected at approximately the same time as dosing for Day 2 (postdose) and Day 7 (postdose) while the Day 14 collection should occur immediately prior to the PET scan.

Administration of ^{18}F-DOPA will occur at the start of the PET scan session. Clinical assessments as described in the Schedule of Assessments (SOA) will be performed.

Follow-up/End of Study (EOS) (7± 2 days after last dose of study drug): A follow-up visit will occur 7 days (± 2 days) after last dose of study drug. Clinical assessments as described in the Schedule of Assessments (SOA) will be performed.

Early Termination: Subjects who discontinue early from the study will complete an early termination visit. Clinical assessments as described in the Schedule of Assessments (SOA) will be performed.

7.2. Treatment Assignment and Blinding

This is a non-randomized study. All subjects will receive SEP-363856 50 mg/day on Day 1 through Day 3. On Day 4, subjects will titrate up to a dose of 75 mg/day. A one-time dose reduction (from 75 mg to 50 mg) for tolerability purposes is permitted and may occur at any time, at the principal Investigator's discretion.

7.3. Rationale

7.3.1. Rationale for the Study Design

This is an open-label, flexibly-dosed, study evaluating the effect on brain dopamine synthesis capacity as measured by ^{18}F-DOPA PET imaging of adjunctive open-label administration with SEP-363856 (50 to 75 mg/day) over 2 weeks in adults with schizophrenia. The 2-weeks of treatment will provide an adequate timeframe within which to evaluate the effects of SEP-363856 in this subject population.

Patients with schizophrenia and other psychotic disorders show altered presynaptic dopaminergic function, as supported by the use of PET-imaging techniques (Jauhar-2017). The radiotracer ^{18}F-DOPA has been commonly used to measure dopamine turnover in PET studies and has consistently reported elevated K_i values in patients with schizophrenia with a summary effect size of 0.8 on meta-analysis, and effect sizes of 1.1 - 1.3 with the current high-resolution PET scanners. Several lines of evidence suggest that increased presynaptic dopamine synthesis capacity and greater baseline dopamine dysfunction are associated with responsiveness to D2-based antipsychotic treatments (Howes-2014). On the other hand, it has been hypothesized that treatment resistance may be linked to a different underlying neurobiology which is more glutamatergic and less dopaminergic. This is supported by the finding that pre-synaptic

dopamine synthesis capacity has been shown to be reduced in treatment resistant schizophrenia (Demjaha-2012, Kim-2017). Given that up to 30% of the schizophrenic population is treatment-resistant, this is an area of significant unmet need, and treatments focused on alternative targets to the D2 receptor are therefore of great interest.

Trace Amine-Associated Receptor 1 (TAAR1) agonists have come to light in recent years as potential targets for the treatment of schizophrenia and related psychotic disorders. With the development of highly selective ligands, there is evidence to suggest that TAAR1 agonists may act as negative modulators of dopaminergic signaling within the mesolimbic system where they are predominantly expressed (Rutigliano-2018). On the basis of PET imaging experiments in animal models, Study SEP361-118 is designed to investigate the effect of SEP-363856 administration adjunctive to an antipsychotic on striatal dopamine synthesis capacity, as measured using ^{18}F-DOPA PET imaging.

^{18}F-DOPA has been used in clinical PET studies to reliably detect dopamine synthesis capacity and therefore will be used as the imaging ligand in this study.

7.3.2. Rationale for the Dosages

Study SEP361-118 will employ a flexible dosing regimen. After initiation at aSEP-363856 dose of 50 mg/day for 3 days, subjects are required to titrate up to 75 mg/day. Subjects may reduce the dose once to 50 mg/day for tolerability reasons at any time. Subjects who have a dose reduction for tolerability will continue to receive the reduced dose for the remainder of the study. This dosing scheme is nearly identical to the dosing regimen utilized in the current, clinically complete Phase 2 study in patients with schizophrenia (Study SEP361-201).

SEP-363856 50 mg/day and 75 mg/day were selected based on the safety and tolerability observed profiles for single and multiple oral doses of SEP-363856 given to healthy adult male subjects and adult subjects with schizophrenia during the clinical development program. Results of completed studies demonstrated that the maximum tolerated single SEP-363856 dose was 50 mg for healthy adult volunteer subjects and 100 mg for adults with schizophrenia. Single doses of SEP-363856 were also shown to have robust central nervous system (CNS) activity in completed fMRI study (SEP361-104). Dose selection is further supported by safety and tolerability results after dosing with SEP-363856 10 mg - 100 mg/day for 7 days and dosing with SEP-363856 75 mg/day for 28 days in adults with schizophrenia (Study SEP361-106, Parts 1 and 2).

The PET ligand ^{18}F-DOPA will be used at each of the PET scans in this study. Up to 150 MBq of ^{18}F-DOPA will be intravenously administered at the start of each PET scan. The total radiation exposure from each PET scan is up to 3 mSv, and each PET scan will be accompanied by up to 2 low dose CT scans resulting in up to 0.7 mSV. The total effective dose from this study is therefore up to 3 * (3.0 + 0.7) = 11.1 mSv, placing it in the III category of the International Commission on Radiological Protection (ICRP) classification, suitable for research studies in human subjects. The effective dose of 11.1 mSv is equivalent to 4.8 years of naturally occurring background radiation. For an adult in good health, this is calculated to result in a risk of approximately 1 in 1800 in induction of fatal cancer. This dose has been selected as it provides images of suitable quality while minimizing the radiation exposure to participants. The majority of participants will receive up to 2 PET scans, which would result in an effective dose of

7.4 mSv. Participants will only receive 3 PET scans in the event that a scan is not able to be completed or is not suitable for analysis.

One hour prior to each PET scan, single doses of 150 mg carbidopa and 400 mg entacapone will be given orally to reduce the peripheral metabolism of ^{18}F-DOPA, and the formation ^{18}F-DOPA metabolites, thereby improving the quality of the acquired brain images. Both drugs are approved at the doses administered for human use and will be administered approximately one hour before the scan. No drug interaction concerns are anticipated with the limited exposure to carbidopa and entacapone.

7.3.3. Rationale for the Study Population

SEP-363856 is a central nervous system (CNS)-active compound which shows broad efficacy in animal models of schizophrenia (positive and negative symptoms), cognition, and depression. The molecular target responsible for these effects has not been completely elucidated but may include actions at 5-HT$_{1A}$ 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 fMRI experiments, pretreatment with SEP-363856 reduced the ketamine brain fMRI response in rhesus monkey, similar to risperidone, supporting an antipsychotic-like profile. ^{18}F-DOPA PET imaging showed that SEP-363856 reduces striatal dopamine synthesis capacity to a greater extent in mice with a state of hyperdopaminergia (induced by sub-chronic ketamine administrations) than in control animals. Taken together, these data demonstrate that SEP-363856 exhibits CNS pharmacodynamic signals in rodents and nonhuman primates consistent with antipsychotic activity, and that SEP-363856 has a pharmacological effect on presynaptic dopamine synthesis capacity.

As of 24 Sept 2018, a total of 246 subjects have received oral doses of SEP-363856 in 8 completed Phase 1 studies. An additional 199 subjects received oral doses of SEP-363856 in ongoing phase 2 studies (placebo-controlled study SEP361-201 and open label extension SEP361-202) and 24 subjects in an ongoing phase 1 study (multiple ascending dose study DA801004 in Japanese subjects) in subjects diagnosed with schizophrenia.

Single doses of SEP-363856 were shown to have robust CNS activity in a completed fMRI Study (SEP361-104) in healthy adult subjects.

The treatment emergent AEs (TEAEs) that were reported in the Phase 1 clinical trials involving SEP-363856 having two-fold higher incidence with SEP-363856 compared with placebo and that were at least possibly related to SEP-363856 in ≥ 2 subjects were classified as adverse drug reactions (ADRs). ADRs to SEP-363856 included nausea, dizziness, and orthostatic hypotension (very common ≥ 10%); and dry mouth, fatigue, lethargy, and sedation (common ≥ 1% and < 10%).

One randomized, double-blind study (SEP361-201) evaluating efficacy and safety of flexible SEP-363856 doses (50 mg/day or 75 mg/day) in adult subjects with schizophrenia is clinically complete clinical study report pending. Subjects completing this study are eligible to enroll in an ongoing 26-week-long-term open-label safety and tolerability study (SEP361-202, ongoing).

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who withdraw consent prior to study completion, the number of visits and assessments has been limited to those required to collect the information needed to address the objectives of the study. The number of PET scans and collection of blood samples are essential components of the study, therefore, subjects will remain in the overnight confinement unit until the completion of the postdose PET scans and blood sample collection (all assessments will be performed in the clinic).

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

A concerted effort by the clinical team will be made to enroll subjects with good venous access. In addition, every effort will be made to have subjects return for the end of study visit to collect follow-up safety data. In the case of failure to obtain adequate data from a measure (eg due scan failure due to technical reasons), the measure may be repeated if feasible (total radiation dose to remain within guidelines for exposure for research purposes).

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

To qualify for participation, subjects must meet all of the following inclusion criteria at screening and Day 1 (including all available predose assessments):

1. Subject must give written informed consent and privacy authorization prior to participation in the study.
2. Subject must be willing and able to comply with the study procedures and visit schedule, including required minimum 2-week in-clinic treatment period, and must be able to understand and follow verbal and written instructions.
3. Male or female subject between 18 to 45 years of age (inclusive) at the time of consent.
4. Subject meets Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for a primary diagnosis of schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the Structured Clinical Interview for DSM-V Clinical Trials Version [SCID-CT]). The duration of the subject's illness whether treated or untreated must be ≥ 6 months.
5. Subject must be on a stable dose of a single antipsychotic medication, dosed within the labeled dose-range, for a minimum of 3 weeks prior to the PET scan at the screening visit. Patients taking clozapine are not eligible to participate.
6. Subject must have a Clinical Global Impression-Severity (CGI-S) score ≥ 3 (mild or greater).
7. Subject must have a Positive and Negative Syndrome Scale (PANSS) total score ≥ 70.
8. Subject's BMI must be at least 18 kg/m^2 but no more than 35 kg/m^2.
9. Female subjects must have a negative serum pregnancy test at screening; as well as a negative urine pregnancy test prior to the PET scan on each day PET scans are performed, as well as prior to the MRI scan.
    a. Female subject of childbearing potential and male subject with female partner of childbearing potential must agree to use a highly effective form of birth control (refer to Section 10.5) from at least 30 days prior to administration of the first dose of study drug, during the treatment period, and 60 days after completion or premature discontinuation from the study drug. Male subjects must also refrain from semen/sperm donation 30 days prior to administration of the first dose of study drug, during the treatment period, and 60 days after completion or premature discontinuation from the study drug.
    In the Investigator's judgment, the subject will adhere to this requirement.
    b. Female subjects who are of non-childbearing potential are not required to abide by birth control requirements.
        – Non-childbearing potential is defined as subject who is surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or is postmenopausal (defined as at least 12 months of spontaneous amenorrhea

[follicle stimulating hormone [FSH] concentrations may be used to confirm a post-menopausal state at the discretion of the investigator, but 12 months of amenorrhea is still required]).

10. Subject is, in the opinion of the Investigator, generally healthy based on screening medical history, PE, neurological examination, vital signs, clinical laboratory values (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, and serum prolactin).
11. Subject has had a stable living arrangement at the time of screening and agrees to return to a similar living arrangement after discharge. This criterion is not meant to exclude subjects who have temporarily left a stable living arrangement (eg, due to psychosis). Such subjects remain eligible to participate in this study. Chronically homeless subjects should not be enrolled.
12. Subject must agree to comply with all medication restrictions for the required length of time (see Concomitant Medication section below).

8.2. Subject Exclusion Criteria

To qualify for participation, subjects must not meet any of the following exclusion criteria at Screening and Day 1 (including all available predose assessments):

1. Subject answers “yes” to “Suicidal Ideation” Items 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 at or during the Screening period (ie, in the past one month) and/or Day 1 (ie, since last visit).
2. Subject does not tolerate venipuncture or has poor venous access that would cause difficulty for administration of the radioisotope and for collecting blood samples.
3. Subject is currently participating in, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent, or has participated in more than 2 studies of investigational compounds within 24 months prior to signing the informed consent.
4. Subject has participated in a research and/or PET or radiological investigations with radiation exposure that, when combined with the dose from the present study, would exceed 10 mSv in addition to natural background radiation, in the previous 12 months.
5. Subject has previously received SEP-363856.

6. Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in the study:
    a. Clinically significant hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular, hepatic, neurologic, or allergic disease (except for untreated, asymptomatic, seasonal allergies at time of dosing).
    b. Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Subject has a pituitary tumor of any duration.
    c. Disorder or history of a condition, or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, bowel resection) that may interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH, or a history of clinically significant abnormality of the hepatic or renal system, or a history of malabsorption.
    d. Subject currently has or has had within the last 6 months a diagnosis of Alcohol or Substance Abuse Disorder (DSM-5 criteria). The only exceptions include caffeine or nicotine.
    e. Subject has a clinically significant abnormal 12-lead ECG that may jeopardize the subject's ability to complete the study as determined by the Investigator or a screening 12-lead ECG demonstrating any one of the following: heart rate > 100 beats per minute, QRS > 120 ms, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 ms (males), QTcF > 470 ms (females), or PR > 220 ms.
    f. Subjects with known history of human immunodeficiency virus (HIV) seropositivity.
    g. Subject has a history of clinically significant hypotensive disorder, systolic blood pressure ≤ 80 mmHg or diastolic blood pressure ≤ 40 mmHg at any measurement prior to dosing on Day 1, or any clinically significant symptoms associated with hypotension at any time during participation prior to dosing on Day 1
7. Female subject who is pregnant or lactating.
8. Subject has a presence or history of a medically diagnosed, clinically significant psychiatric disorder (including intellectual disability, major depressive disorder with psychosis, and bipolar disorder) other than schizophrenia (medically diagnosed schizoaffective disorder or schizophreniform disorder will be allowed).
9. Subject tests positive for drugs of abuse at screening, however, a positive test for barbiturates, opiates, benzodiazepines or methadone may not result in exclusion of subjects if the Investigator determines that the positive test is as a result of prescription medicine(s). In the event a subject tests positive cannabinoids (tetrahydrocannabinol), the Investigator will evaluate the subject's ability to abstain from using this substance during the study. This information will be discussed with the Medical Monitor prior to study enrollment.
10. Subject is at significant risk of harming him/herself or others according to the Investigator's judgment.
11. Subject has attempted suicide within 6 months prior to screening.

12. Subject is involuntarily hospitalized.
13. Subject is judged in the opinion of the Investigator to be severely resistant to antipsychotic treatment defined as a failure to respond to 4 or more marketed antipsychotic agents, given at an adequate dose as per labeling and for an adequate duration (lifetime).
14. Subject is receiving an antipsychotic medication at a dose above the maximum labeled dose (country-specific) for less than 12 weeks prior to the PET scan at the screening visit.
15. Subject has received clozapine treatment within 120 days of planned PET scan at screening.
16. Subject has received electroconvulsive therapy treatment within the 3 months prior to screening or is expected to require ECT during the study.

(Note: Criteria 17 intentionally skipped)

18. Subject has a history of allergy or hypersensitivity to more than 2 distinct chemical classes of drug (eg, sulfonylureas and penicillins) or suspected sensitivity to any substance that is contained in the study drug formulation or to carbidopa or entacapone.
19. Subject has any clinically significant abnormal laboratory values as determined by the Investigator (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, and serum prolactin). (Note: abnormal findings of questionable significance will be discussed with the Medical Monitor prior to including subject).
20. Subject demonstrates evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation.

    Note: Subjects with serum alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 3 times the upper limit of the reference ranges provided by the laboratory require retesting. If on retesting, the laboratory value remains ≥ 3 times the upper limit, the subject will be excluded.
21. Subject has bilirubin ≥ 1.5 x upper limit of normal (ULN) with the exception that isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractioned and direct bilirubin < 35% at screening.
22. Subject has a serum blood urea nitrogen (BUN) or serum creatinine (Cr) value ≥ 1.5 times the upper limit of normal for the reference range.
23. Subject has experienced significant blood loss (≥ 473 mL), has donated blood within 60 days prior to first dose of study drug, has donated plasma within 72 hours prior to the first dose of study drug or intends to donate plasma or blood or undergo elective surgery during study participation or within 60 days after the last study visit.
24. Subject consumes more than 300 mg of caffeine per day (5 cups of coffee or equivalent in caffeinated beverages).
25. Subject has used disallowed prescription or disallowed nonprescription drugs, or dietary or herbal supplements as specified within the Concomitant Medications and Restrictions (Section 10.3) for at least 5 half-lives or 14 days prior to dosing, whichever is longer, or

anticipates the need for any disallowed medication during their participation in this study (exception: female subjects who are taking oral, patch, or intrauterine device [IUD] hormonal contraceptives, or progestin implant or injection). Further details to be provided in Section 10.3.

26. Subject is a staff member or the relative of a staff member.
27. Subject is in the opinion of the Investigator, unsuitable in any other way to participate in this study.
28. Subject has contraindications to undergoing MRI/fMRI examination including, but not limited to claustrophobia, metal foreign bodies or implanted devices incompatible with the MRI/fMRI exposure.

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
Dosage form	Tablet	Tablet
Unit dose	50 mg	75 mg
Route of administration	Oral	Oral
Physical description	Yellow oval tablet	Yellow oval tablet
Active Pharmaceutical ingredient (API)	SEP-363856-01(hydrochloride salt)	SEP-363856-01 (hydrochloride salt)
Excipients	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax	-Microcrystalline cellulose -Mannitol -Sodium starch glycolate -Magnesium stearate Film coating: -Hydroxypropyl methylcellulose -Hydroxypropyl cellulose -Titanium dioxide -Yellow iron oxide Carnauba wax

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

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

9.2.2. Labeling Description

All packaging for the study drugs will be labeled with:

- Protocol number
- Sponsor's name and address
- Compound/Code or name of investigational drug and dosage form
- Contents (eg number of tablets)
- Investigational drug/Caution statement
- Instructions for use and storage
- Batch number
- Blank space for subject identifiers

- Period of use (as required)
- Unique medication/kit ID number
- Investigator information (if needed)

9.3. Study Drug Storage

All SEP-363856 tablets are to be stored at controlled room temperature, between 15°C and 25°C (59°F and 77°F).

9.4. Dispensing of Study Drug

Study drug will be administered on an in-patient basis as open-label 50 mg or 75 mg dosage strengths of SEP-363856. Subjects will take one tablet of study drug per day at approximately the same time each day with morning dosing recommended. Dosing may be moved to the evening for reasons of tolerability; except for the day of post dose fMRI scanning where dosing will occur approximately 2 to 4 hours before fMRI scanning. Study drug may be taken without regard to food.

Appropriate guidelines should be followed in proper dispensation to the study participant. Study drug will not be dispensed to any person who is not a study subject under this protocol.

9.5. Study Drug Accountability

The Investigator or designee is responsible for maintaining adequate and up to date records of drug disposition that include the dates, quantities received and dispensed, and use by subjects.

Upon receipt of study drug, the Investigator or designee will inspect the supplies and confirm receipt of the shipment. The Investigator or designee will review the contents of each drug shipment against the provided packing list and confirm date of receipt, completeness of shipment and condition of study drug received.

9.6. Study Drug Handling and Disposal

The Investigator or designee is responsible for storing the study drug in a secure location. Study drug should be maintained under the strict control of qualified site staff at all times. Proper storage and handling guidelines should be followed. An Investigational Product (IP) Manual will be supplied. In the event that study drug expires while at the site before it is returned to the depot, the Investigator or designee should store the expired study drug separately.

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

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

10. TREATMENT OF SUBJECTS

10.1. Study Medication

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

Subjects may take study drug with or without food. Study drug (Days 1 – 13) should be taken at approximately the same time each day with morning dosing recommended. Dosing may be moved to the evening for reasons of tolerability; except for the day of post dose fMRI scanning where dosing will occur approximately 2 to 4 hours before fMRI scanning.

10.1.1. Dose Adjustment Criteria

Subjects will receive SEP-363856 50 mg/day on Day 1 through Day 3. On Day 4, subjects will titrate up to a dose of 75 mg/day. Subjects may dose reduce one time to 50 mg/day for tolerability reasons at any time. Subjects who have a dose reduction for tolerability will continue to receive the reduced dose for the remainder of the study.

10.2. Treatment Compliance

Study drug will be administered in-clinic. The Investigator will record the dose of the study drug and the dates of the initial and final administration for each dose.

10.3. Concomitant Medications and Therapies

The following information on all medication administered between screening and end of study or at discontinuation will be recorded on the case report form (CRF): Medication name, dose, frequency, route, start date, stop date, and indication.

Prior treatment with antipsychotic agents including depot neuroleptics will be recorded for at least 6 months prior to the screening visit. All other prior treatments will be recorded for at least 3 months prior to screening.

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).

Subjects who require treatment with a prohibited concomitant medication will be discontinued from the study.

10.3.1. Prohibited Medications

Concomitant use of CYP2D6 inhibitors is prohibited as SEP-363856 is a potential substrate for CYP2D6.

All psychotropic medications and herbal supplements (with the exception of the single, background antipsychotic, or medications listed in Section 10.3.4) are prohibited during the study and must be discontinued, as tolerated and clinically appropriate (for at least 5 half-lives or 14 days, whichever is longer), prior to the first dose of study drug in a manner that is consistent with labeling recommendations and conventional medical practice.

Clozapine is prohibited. Prior exposure to clozapine is allowed, as long as treatment is discontinued at least 120 days prior to PET scan at screening.

Subjects who require treatment with one or more of the prohibited concomitant medications (including antidepressants, mood stabilizers, or anxiolytics [lorazepam or equivalent at doses above protocol-specified limits]) will be discontinued (as appropriate) from the study.

All efforts will be made to complete the PET and resting state fMRI scans intended by the protocol even in cases of discontinuations of study drug or procedures.

The majority of participants will receive up to 2 PET scans. Participants will only receive 3 PET scans in the event that a scan is not able to be completed or is not suitable for analysis.

10.3.2. Prohibited Therapies

Electroconvulsive therapy (ECT) is prohibited within 3 months prior to screening and during the study.

10.3.3. Restricted Medications

Caution should be taken with concomitant use of CYP2D6 substrates with SEP-363856 as SEP-363856 is a weak inhibitor of CYP2D6 (see to Section 25).

Concomitant Non-psychotropic Medications:

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after enrollment if the dose and regimen have been stable (± 25%) for at least 30 days prior to screening. The concomitant medication dose may change, as needed, after enrollment (or be discontinued). β-adrenergic antagonists used to treat stable hypertension may be continued through the screening phase and post-initiation. Medications for short-term treatment of a medical condition (no more than 10 days) are allowed during the study with consultation with the Medical Monitor.

Concomitant Psychotropic Medications:

Treatment with benztropine 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) or procyclidine (up to 30 mg/day). Treatment with propranolol (up to 120 mg/day) will be permitted as needed for akathisia.

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

1. 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.

2. temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zaleplon (≤ 20mg/day), zolpidem (≤ 10 mg/day), and zolpidem CR (≤ 12.5 mg/day) may be administered at bedtime for insomnia, as needed.
3. 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 sedative/hypnotic 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).

Similar drugs at equivalent dosages will be permitted as described in the Operations Manual or in consultation with the Medical Monitor.

10.3.4. Permitted Medications

Subjects must be on a stable dose of a single antipsychotic medication, dose within the labeled dose-range, for a minimum of 3 weeks or if above the maximum label dose (country specific) for at least 12 weeks prior to the PET scan at the screening visit, and the dose should remain fixed throughout the study. Depot neuroleptic dose must be stable for at least 2 treatment cycles or at least 30 days (whichever is longer) prior to the screening visit.

Subjects who require an increase in dose of their background antipsychotic during the study will be discussed with the Medical Monitor. A down-titration of the background antipsychotic due to tolerability may be allowable, after consultation with the study medical monitor.

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. Hydrocortisone 1% cream or ointment for treatment of contact dermatitis from ECG pads is allowed. Female subjects may use oral, patch, or intrauterine device (IUD) hormonal contraceptives, or progestin implant or injection (detailed information on allowed contraceptives provided in Section 10.5).

10.4. Restrictions

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

10.5. Contraception Requirements

Female subject of childbearing potential and male subject with female partner of childbearing potential must agree to use a highly effective form of birth control from 30 days prior to administration of the first dose of study drug, during the treatment period, and 60 days after completion or premature discontinuation from the study drug. Male subjects must also refrain from donation of semen/sperm 30 days prior to administration of the first dose of study drug, during the treatment period, and 60 days after completion or premature discontinuation from the study drug. Continued use of a highly effective form of birth control for males and females is recommended for 2 months after study completion or discontinuation from the study.

Methods that can achieve a failure rate of less than 1% per year when consistently and correctly used are considered as highly effective. Such methods are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (with surgical success confirmed by medical assessment)
- Sexual abstinence if part of the volunteers preferred lifestyle

Hormonal contraceptives have the following timeframe requirements:

a) Contraceptive implant implanted at least 90 days prior to screening;

b) Injectable contraception given at least 14 days prior to screening; or

c) Oral contraception taken as directed for at least 30 days prior to screening.

Female subjects who are of non-childbearing potential are not required to abide by birth control requirements.

Non-childbearing potential is defined as a subject who is surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or is postmenopausal (defined as at least 12 months of spontaneous amenorrhea) are not required to remain abstinent or use adequate contraception.

10.6. Dietary Guidelines

While subjects are confined to the clinic, meals will be provided. Subjects will receive meals according to the study site procedures.

11. STUDY ASSESSMENTS

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

11.1. Demographics and Baseline Characteristics

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

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

11.2. Prior and Concomitant Medication Review

See Section 10.3 for a complete description of medications permitted during the study. Site study staff will record all medications used to treat schizophrenia taken within 6 months prior to screening visit in the eCRF. Also, the following parameters will be recorded for all concomitant medications: drug name, route of administration, total daily dose, unit, frequency, start/stop dates, indication, and whether the medication was started after last dose of study medication. The prior and concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

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

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

11.4. PET/fMRI Assessments

It is important that the participant is examined under the same conditions at baseline and subsequent scan, including scanning at the same time of day where possible (scanning time of day should be ± 3h from the time of day of the baseline scan where possible), and head motion monitored and minimised. The post-dose scan should be timed to occur so that the start is approximately at the time in which maximum observed plasma concentration (C_{max}) occurs. Post dose fMRI scanning will start approximately 2 to 4 hours after dosing.

Prior to entry into the scanner, subjects will complete the site's standard radiography screening questionnaire to ensure they are safe to enter the scanner environment (eg, no history of surgery involving metal implants). Females will undergo urine pregnancy test to exclude pregnancy. Scan date as well as start and stop time will be collected.

Approximately 1 hour before the scan participants will receive 150 mg of carbidopa and 400 mg of entacapone orally. This inhibits the formation of radiolabeled metabolites of F-DOPA that may cross the blood-brain barrier, and boosts the signal to noise ratio. Subjects will have an IV canula placed in the ante-cubital fossa for administration of F-DOPA. Prior to scanning they will be asked to go to the toilet.

Striatal dopamine synthesis capacity (DSC) assessment (Ki) using ^{18}F-DOPA kinetic analysis will be performed.

In addition to fMRI scan sequences, exploratory MRI sequences may be performed during each of the MRI and PET/MR acquisition times and may include (but not limited to) a neuromelanin-sensitive MRI (NM-MRI) sequence and an iron-sensitive MRI sequence (effective transverse relaxation rate [R2*] or Quantitative Susceptibility Mapping [QSM]). Repeat MRI including exploratory MRI sequences may be performed where it is not possible to obtain complete measures during the PET-MRI scan.

The majority of participants will receive up to 2 PET scans. Participants will only receive 3 PET scans in the event that a scan is not able to be completed or is not suitable for analysis.

11.5. Efficacy Assessments

11.5.1. Positive and Negative Syndrome Scale (PANSS)

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

11.5.2. 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.

11.5.3. 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.

11.5.4. 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.

11.6. Safety Assessments

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

11.6.1. 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.

11.6.2. Clinical Laboratory Assessments

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

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed locally. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the study center and local clinical laboratory guidelines. Samples will be processed at a local laboratory.Out of range laboratory results assessed as clinically significant by the investigator will be reported as adverse events.

11.6.3. Vital Signs

Vital sign measurements consist of systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature.

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 results assessed as clinically significant by the investigator will be reported as adverse events. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

11.6.4. Electrocardiograms (ECGs)

Subjects will be supine for at least 10 minutes prior to and 5 minutes after the ECG is obtained. 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 not clinically significant (NCS) or clinically significant (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.

11.6.5. Physical and Neurological Examination

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

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

11.6.6. Height, Weight, and BMI

Weight will be measured in kilograms as specified in the schedule of assessments (Table 2). Height in meters will be recorded only at Screening.

Height will be measured without shoes.

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

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

11.6.7. Safety Scales

11.6.7.1. 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.

11.6.7.2. 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.

11.6.7.3. Simpson-Angus Scale (SAS)

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

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

The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the trial. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to

administer. The C-SSRS will be administered by a trained rater at the site. Subjects with Type 4 or Type 5 suicidal ideation during the study will be discontinued from the study and referred to a mental health professional (Posner-2007). At screening visit, "Baseline/Screening" version of C-SSRS will be used including assessment for lifetime and previous 1 month. For all visits from Visit 2 onward, the "Since Last Visit" version of the C-SSRS will be used.

11.7. 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 doses of study drug, date, and clock time of sampling must be recorded. Date and clock time of food intake must be recorded when blood samples are collected for determination of plasma SEP-363856 and SEP-363854 concentrations. Plasma SEP-363856 and SEP-363854 concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Population pharmacokinetic (POP-PK) 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 22 Appendix III for details including instructions of processing blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations.

All blood samples for determination of plasma antipsychotic concentrations will be obtained at the same time that other blood samples are taken whenever possible. The time and date of doses of antipsychotic medication, date, and clock time of sampling must be recorded. See Section 23 Appendix IV for details including instructions of processing blood samples for determination of plasma concentrations.

11.8. Pharmacogenomic Assessments

If a subject has consented to have a deoxyribo nucleic acid (DNA) sample taken for genetic analysis (and is eligible for randomization), a blood sample (approximately 4 mL) for pharmacogenetic (PGx) analysis will be taken. Samples should not be collected if the subject has not consented to PGx sampling. If samples are collected for analysis, this analysis must be performed. The timing of the analysis may be following completion of this study and as such can be reported separately. Blood samples will be shipped to the central laboratory where they will be stored frozen until shipment to the PGx laboratory (contact details provided in the general study information section of the protocol). Following shipment, DNA will be extracted and the PGx laboratory will remain blinded to the identity of the subject, but will have access to information relating to demographics of the subject (ethnic origin and gender). See Section 24 Appendix V for details including instructions of PGx sample handling.

11.9. Study Visits and Assessments

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

11.9.1. Screening (Day -49 to Day -2): Visit 1

A unique screening number will be assigned to each subject.

Subjects will be evaluated at the Screening Visit to determine their eligibility to enroll in the study. No imaging procedures involving ionizing radiation will be performed within 12 hours of written consent.

Procedures may be completed in any order unless specified otherwise.

The following study-related procedures will be performed at Screening (procedures will occur over multiple days):

- Obtain signed informed consent and privacy authorization from the subject before conducting any other visit procedures.
- Inclusion and exclusion criteria
- Obtain demographic information.
- Prior/concomitant medications
- Medical history
- Psychiatric history/mental status
- SCID-CT
- Physical examination.
- Height and weight; clinical site staff to calculate and record BMI.
- Vital sign measurements.
- Perform ECG.
- Collect blood sample for clinical laboratory evaluation (hematology, chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], Hepatitis B/C, HIV-1/HIV-2, and fasted glucose panel and lipid panel).
- Collect blood samples for serum pregnancy test (serum human chorionic gonadotropin [β-hcG]) for female subjects and serum follicle stimulating hormone (FSH) for female subjects if menopause is suspected.
- Collect blood sample for antipsychotic levels.
- Collect urine sample for urinalysis and urine drug screen (UDS).
- Perform MRI (MRI at screening must occur prior to the PET scan at screening).
- Perform psychiatric assessments in the following order: PANSS, BNSS, C-SSRS, CGI-S.
- Collect adverse events.
- Perform PET/MR Scan including fMRI (Day -44 to Day -2). Approximately 1 hour before the scan participants will receive 150 mg of carbidopa and 400 mg of entacapone orally.

- Female subjects only, collect urine samples for pregnancy test (any positive test must be followed up with a serum β-hcG test). Urine pregnancy test to be performed on the same day as, but prior to, screening PET/MR Scan.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator. Subjects who screen fail due to MRI or PET or fMRI results may not be re-screened.

Re-screened subjects will be re-consented and all screening procedures will be repeated except:

- SCID results from the original screening will be reviewed and updated if necessary.
- MRI (without any abnormality) obtained at the study's imaging center within 90 days prior to Day -1 check-in is acceptable for eligibility.

11.9.2. In-Clinic (Day -2 to Day 14): Visit 2

11.9.2.1. Day -2, Check-in

The following procedures will be conducted for this Visit Day:

- Review Inclusion/exclusion criteria.
- Concomitant medications.
- Vital sign measurements
- Weight
- Perform ECG.
- Collect blood sample for clinical laboratory evaluation (hematology, chemistry, serum prolactin, and fasted glucose panel and lipid panel).
- Collect blood sample for antipsychotic levels.
- Collect urine sample for urinalysis and urine drug screen (UDS).
- Female subjects only, collect urine samples for pregnancy test (any positive test must be followed up with a serum β-hcG test).
- Collect adverse events.

If the subject still qualifies for the study after completion of study day procedures; the subject will be checked into the clinic.

11.9.2.2. Day -1

The following procedures will be conducted for this Visit Day:

- Review Inclusion/exclusion criteria.
- Concomitant medications
- Vital sign measurements

- Perform psychiatric assessments in the following order: PANSS, BNSS, MADRS, CGI-S. (May be collected on Day -2)
- Perform C-SSRS. (May be collected on Day -2)
- Collect adverse events.

11.9.2.3. Day 1

All procedures should occur prior to dosing unless specified otherwise.

The following procedures will be conducted for this Visit Day:

- Review Inclusion/exclusion criteria.
- Collect concomitant medications.
- Vital sign measurements
- Weight
- Perform ECG
- Female subjects only, collect urine samples for pregnancy test (any positive test must be followed up with a serum β-hcG test) (must be performed predose).
- Collect blood sample for determination of plasma SEP-363856 and SEP-363854 concentration.
- Collect blood sample for antipsychotic levels.
- Collect blood sample for pharmacogenomics.
- Collect urine sample for urine drug screen (UDS).
- BARS (May be collected on Day -1)
- AIMS (May be collected on Day -1)
- SAS (May be collected on Day -1)
- Collect adverse events.
- Dispensation of blister card
- Administer study drug.

11.9.2.4. Day 2

The following procedures will be conducted for this Visit Day:

- Collect blood sample for determination of plasma SEP-363856 and SEP-363854 concentration. (collected approximately 2-4 hours postdose)
- Collect blood sample for antipsychotic levels. (collected approximately 2-4 hours postdose)
- Concomitant medications

- Collect adverse events
- Administer study drug

Daily administration of study drug, monitoring of adverse events and concomitant medications will continue for Days 3 through 6.

11.9.2.5. Day 7

The following procedures will be conducted for this Visit Day:

- Collect blood sample for determination of plasma SEP-363856 and SEP-363854 concentration. (collected approximately 2-4 hours)
- Collect blood sample for antipsychotic levels. (collected approximately 2-4 hours postdose)
- Concomitant medications
- Collect adverse events.
- Administer study drug.

Daily administration of study drug, monitoring of adverse events and concomitant medications will continue for Days 8 through Day 13.

Note: Dispensation of blister card on Day 8.

11.9.2.6. Day 14 (+5 Days)

All Day 14 assessments are to be completed the same day as the PET scan, unless otherwise noted. The following procedures will be conducted on the Day 14 PET scan day:

- Collect concomitant medications.
- Vital sign measurements.
- Weight
- Perform ECG.
- Collect blood sample for clinical laboratory evaluation (hematology, chemistry, serum prolactin, and fasted glucose panel and lipid panel).
- Female subjects only, collect urine samples for pregnancy test (any positive test must be followed up with a serum β-hcG test) (must be performed predose).
- Collect urine sample for urine drug screen (UDS).
- Perform psychiatric assessments in the following order: PANSS, BNSS, MADRS C-SSRS, CGI-S.

  Note: PANSS, BNSS, MADRS, and CGI-S assessments may be collected ± 1 day of PET Scan; however, C-SSRS must be performed same day as PET Scan.
- BARS

- AIMS
- SAS
- Collect adverse events.
- Administer study drug.
- Collect blood sample for determination of plasma SEP-363856 and SEP-363854 concentration immediately prior to fMRI scan.
- Collect blood sample for antipsychotic levels immediately prior to fMRI scan.
- Perform PET/MR Scan including fMRI. Approximately 1 hour before the scan participants will receive 150 mg of carbidopa and 400 mg of entacapone orally.
- Discharge subject from clinic after all Day 14 assessments are complete.

In the event of an unsuccessful PET scan on Day 14, additional days of dosing may be necessary up to, but not exceeding, Day 19. If any such additional days of dosing are necessary, subjects will continue their usual daily dosing with monitoring of adverse events and concomitant medications. All Day 14 assessments are to be completed **again** occurring on the same day as the PET scan, unless otherwise noted above.

11.9.3. Outpatient Follow-up / End of Study (EOS) (7 ± 2 Days Post Last Dose of Study Drug): Visit 3

The following procedures will be at this visit:

- Collect concomitant medications.
- Physical examination
- Vital sign measurements
- Weight
- Perform ECG.
- Collect blood sample for clinical laboratory evaluation (hematology, chemistry, serum prolactin, and fasted glucose panel and lipid panel).
- Collect blood sample for determination of plasma SEP-363856 and SEP-363854 concentration.
- Collect blood sample for antipsychotic levels.
- Female subjects only, collect urine samples for pregnancy test (any positive test must be followed up with a serum β-hcG test).
- Collect urine sample for urine drug screen (UDS).
- C-SSRS
- BARS
- AIMS

- SAS
- Collect adverse events.

11.9.4. Early Termination (ET)

The following procedures will be at this visit:

- Collect concomitant medications.
- Physical examination
- Vital sign measurements
- Weight
- Perform ECG.
- Collect blood sample for clinical laboratory evaluation (hematology, chemistry, serum prolactin, and fasted glucose panel and lipid panel).
- Collect blood sample for determination of plasma SEP-363856 and SEP-363854 concentration.
- Collect blood sample for antipsychotic levels.
- Female subjects only, collect urine samples for pregnancy test (any positive test must be followed up with a serum β-hcG test).
- Collect urine sample for urine drug screen (UDS).
- Perform psychiatric assessments in the following order: PANSS, BNSS, MADRS, C-SSRS, CGI-S. (Only perform PANSS, BNSS, MADRS, CGI-S if early termination occurs prior to Day 14 PET/MR scan.)
- BARS
- AIMS
- SAS
- Collect adverse events
- Perform PET/MR Scan including fMRI (only perform if the subject terminates the study prior to the Day 14 PET/MR Scan).

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after signing the informed consent form (ICF), whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from the time of signing the ICF to the last study visit/EOS visit.

New signs and symptoms of underlying disease, or signs and symptoms of emerging disease must be recorded as AEs.

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

12.1.2. Serious Adverse Events

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

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

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

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

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

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

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

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

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

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

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

12.3. Collection and Recording of Adverse Events

All 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 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 from the time of informed consent through 30 days following the last dose of the study medication, 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 the PPD- pharmacovigilance (PVG) if considered at least possibly related to the study drug.

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

An initial or follow-up SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG immediately but not more than 24 hours after the Investigator or study center staff becomes aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Principal Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

12.4.2. Pregnancy

Subject 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 pregnancy is reported for a study subject's partner following the subject's discharge through 90 days following the last dose of study drug, the subject's partner may be asked to sign a consent form to allow Sponsor to follow her pregnancy. The Sponsor's representative will provide instructions on how to collect pregnancy information in accordance with local requirements.

If a subject becomes pregnant during the course of the study, she will be instructed to not take any more study drug. Further, the 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 not receive any additional study medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

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.

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

Subjects may terminate the study participation at any time for any reason.

The possible reasons for the termination of study participation are as follows:

- Adverse event.
- Lost to follow-up (specify).
- Withdrawal by subject (specify).
- Non-compliance with study drug (specify).
- Protocol deviation (specify).
- Pregnancy.
- Death.
- 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 treatment.

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

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

13.2. Clinical Assessments After Study Drug Discontinuation

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

For subjects who have received study drug and who prematurely discontinue from the study treatment (ie, do not complete all visits through Follow-up), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.9.4.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center 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 medications 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 be required to undergo final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.9.4.

15. STATISTICS

15.1. Sample Size

This study is designed to determine the magnitude of a possible pharmacological effect of SEP-363856 on dopamine synthesis capacity. Dopamine synthesis capacity has shown good test-retest reliability (Egerton-2010). Prior studies have reported a within-subject standard deviation of 0.00056/min in dopamine synthesis capacity. The absolute elevation in dopamine synthesis capacity for schizophrenia cases versus normal healthy controls is estimated to be approximately 0.001/min, and to have a correlation of approximately 0.6 with symptoms. Given this relationship between dopamine synthesis capacity and symptoms, it is estimated that a decrease in dopamine synthesis capacity of 0.0005/min in patients is the smallest reduction likely to be clinically significant (anticipated to translate into > 20% reduction in symptoms which is generally considered the smallest change readily detected in clinical practice). A sample size of 16 subjects treated with SEP-363856 will provide > 90% power to detect a treatment reduction of 0.0005/min (change from baseline) in dopamine synthesis capacity using a paired sample t-test and alpha set at the 0.05 level.

Subjects who are initiated on treatment but discontinue from the study may not be replaced. The total sample size will be 22 subjects to allow for up to 25% drop-out to obtain complete PET scans on at least 16 subjects.

15.2. Analysis Populations

The following populations will be defined:

- Safety Population: The safety population will consist of all subjects who receive at least one dose of study drug.
- PET Population: The PET population is defined as all subjects who took at least one dose of SEP-363856 and have a baseline and a post-baseline PET assessment.
- Efficacy population: the efficacy population is defined as all subjects who have received at least one dose of study drug, and have any postdose data for the PANSS, CGI-S, BNSS or MADRS.
- Per Protocol Population: The Per Protocol Population is defined as all subjects in the PET population, the subject completed the study, and the subject had NO important protocol deviations.

15.3. Data Analysis

15.3.1. Subject Disposition

The number and percentage of subjects screened, screen failed, enrolled, dosed, and completing the study will be summarized. The number and percentage of subjects who terminate early will also be summarized, with reasons for early termination.

15.3.2. Drug Exposure and Compliance

A data listing, by subject, containing the study medication dosing and dosing errors, if any, will be provided. Treatment compliance will not be summarized as all dosing will occur in-clinic.

The total number of days of exposure will be summarized categorically (N [%]).

15.3.3. Important Protocol Deviations

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

- Did not meet inclusion/exclusion criteria.
- Received any disallowed concomitant medication.

Individual IPDs will be presented in a data listing. The number and percentage of subjects with IPDs will be summarized by type of deviation and dose group.

15.3.4. Demographic and Baseline Characteristics

Basic demographics (e.g. age, gender, race, ethnicity, etc.) will be summarized descriptively. Medical history will be coded using MedDRA, and will be summarized for the safety population by presenting the number and percentage of subjects with at least one condition in each system organ class (SOC) and preferred term (PT).

15.3.5. Medical History and Psychiatric History

Medical and psychiatric history will be coded using MedDRA. The count and percentage of subjects under each history term, coded by SOC and PT, will be summarized.

15.3.6. Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI) Analysis

The analysis of brain dopamine synthesis capacity and fMRI analysis will use the PET population.

The region of interest in the primary endpoint is the whole striatum. Exploratory analyses will be conducted in other regions and sub-regions of interest. The cerebellum will be used as the reference region. The regions of interest will be delineated on the subjects structural MR based on using the Hammersmith Atlas, and this will be co-registered to the subject's dynamic PET images. Dopamine synthesis capacity will be calculated based on each individual PET images collected at each scan for each subject using a Patlak Graphical Analysis. For the fMRI image pre-processing will be performed via the CONN toolbox (version 17.b)(65) for Statistical Parametric Mapping software (SPM 12 (6906)). For each participant, BOLD signal time-series will be extracted from the nodes in the Gordon cortical atlas, and functional connectivity determined within primary networks of interest (the default mode network, the salience network) and the visual network (a control network), and additional networks guided by the PET analysis.

The primary endpoint is the change from baseline in dopamine synthesis capacity at Week 2 will be calculated, together with 95% confidence interval from a paired sample t distribution.

Changes in resting state BOLD fMRI signal within the salience, default mode, and visual networks at each post-dose time point from baseline will be summarized.

Changes in exploratory MRI markers, including (but not limited to) neuromelanin and iron signal at each post-dose time point from baseline will be summarized.

15.3.7. Efficacy Analyses

Efficacy parameters include PANSS, CGI-S, BNSS, and MADRS. Tabular and graphical summaries will be based on the Efficacy Population.

The actual and changes from baseline at each post-dose time point will be summarized, with 95% confidence intervals. The relationship between dopamine synthesis capacity at baseline and measures of baseline symptom severity (PANSS, CGI-S, BNSS, and MADRS) and their change from baseline will be presented graphically.

15.3.7.1. Subgroup Analysis

Subgroup analyses are not planned for the efficacy parameters.

15.3.8. Safety Analyses

15.3.8.1. Adverse Events

All AEs will be coded using MedDRA.

Treatment emergent AEs (TEAEs) are untoward medical occurrences:

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

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

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

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

The following conventions will be followed in summarizing TEAEs:

- 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 TEAE 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 medication, TEAEs will be grouped as "related" or "not related." TEAEs assessed as "possible," "probable," or "definite," will be grouped as "related." If a subject reports more than one TEAE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related.

Untoward medical occurrences that occur between the time of signing the ICF and first drug administration are pretreatment events.

A listing of all AEs, as well as a listing of deaths, SAEs, or AEs leading to discontinuation, will be presented.

15.3.8.2. Clinical Laboratory Assessments

Laboratory data will be summarized overall for the safety population.

For laboratory parameters with continuous outcomes, descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for the observed values and for changes from baseline will be presented and overall at each visit. For laboratory parameters with categorical outcomes, the number and percentage of subjects with each outcome will be presented for each dose cohort and overall at each visit.

The number and percentage of subjects with Sponsor defined potentially clinically significant (PCS) laboratory values (defined in the SAP) will be summarized for each dose cohort and overall at each visit. The data listings for laboratory parameters will flag values outside of the reference range. Clinically significant laboratory findings will be displayed in a separate data listing.

15.3.8.3. Electrocardiograms

Electrocardiogram parameters to be collected include ventricular heart rate, QT interval, PR interval, QRS duration, and RR interval (ms). The corrected QT interval will be derived according to the Fridericia formula (QTcF) as well as Bazett's formula (QTcB).

ECG data will be summarized overall for the safety population.

Electrocardiogram parameters and changes in these parameters from baseline, as determined by the central over-read, will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) at each visit.

The number and percentage of subjects with QTcF values in the following categories will be summarized:

- QTcF $\geq$ 500 ms at any postdose timepoint and not present at baseline.
- QTcF $\geq$ 480 ms at any postdose time point and not present at baseline.
- QTcF $\geq$ 450 ms at any postdose timepoint and not present at baseline.
- Change from baseline in QTcF $\geq$ 60 ms for at least one postdose measurement.
- Change from baseline in QTcF $\geq$ 30 ms for at least one postdose measurement, but $\leq$ 60 ms for all postdose measurements.

For these categorical analyses, the percent of subjects will be based on the number of subjects with at least one non-missing post treatment value. Any early termination visit or unscheduled ECG that occurs after the single dose will be included for these posttreatment summaries.

The number and percentage of subjects with potentially clinically significant post-baseline values (defined in the SAP) will be presented.

15.3.8.4. Vital Signs

Oral body temperature, respiration rate, pulse (supine and standing) and systolic and diastolic blood pressure (supine and standing) will be summarized overall using descriptive statistics at each visit. Changes from baseline will be summarized in the same manner. The number and percentage of subjects with Sponsor defined PCS vital sign values (defined in the SAP) will be presented overall at each visit.

The number and percentage of subjects with orthostatic hypotension will be summarized by dose cohort by timepoint and overall. Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after the subject had been standing for at least 2 to 4 minutes, compared to the systolic and diastolic blood pressures measured in the supine position, respectively.

15.3.8.5. Physical/Neurological Examination

Findings from the physical and neurological examination will be presented as follows: pre-existing clinically significant conditions recorded as medical history, and new clinically significant conditions recorded as AEs. Physical and neurological examination findings will also be provided in a data listing (date/time of examination and yes/no [was examination performed]).

15.3.8.6. Concomitant Medications

All medications will be coded using WHO-DD.

Medication taken between screening and the follow-up visit will be reported as concomitant. The number and percentage of subjects using each concomitant medication will be summarized overall according to the WHODRUG Anatomic Therapeutic Class (ATC) Level and preferred term. Subjects with multiple uses of a concomitant medication will be counted once by the WHODRUG class and preferred term.

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

A listing of all C-SSRS responses will be provided.

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

15.3.8.8. Movement Disorder Measures

Movement disorder measures include AIMS, BARS, and SAS. The BARS, AIMS, and SAS will be summarized descriptively by presenting summary statistics of actual values and change from baseline values.

15.3.8.9. Subgroup Analysis

No subgroup analyses are planned for the safety parameters.

15.3.9. Pharmacokinetic Analysis

Plasma concentrations of SEP-363856 and its metabolite SEP-363854 will be summarized descriptively at each scheduled sample collection time point.

15.3.10. Interim Analysis

No interim analysis is planned.

15.3.11. Treatment of Missing Data

No imputation will be performed for missing data. Missing data will be considered as missing at random.

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

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results,) will be recorded in the subject's electronic CRF. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulation (CFR) Part 11. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

16.2. Computerized Systems Used for Source Data

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

Table 6: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent	A
Review inclusion/exclusion criteria	A
Demography	A
Prior/concomitant medication review	A
Dispensation of study drug	NA
Administration of Study Drug	A
Admit to Clinic, if not admitted during screening	NA
Clinic Discharge	NA
Medical history	A
Psychiatric history/mental status	A
SCID-CT	A
Physical examination	A
Height/BMI	A
Vital signs	A
Weight	A

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

Protocol Step	Computerized System Type or Description
Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B
Serum prolactin	B
Hepatitis B/C, HIV-1/HIV-2	B
Glycosylated hemoglobin (HbA_{1c})	B
Glucose and Lipid panel	B
Follicle stimulating hormone (FSH), females only	B
Serum human chorionic gonadotropin (β-hCG)	B
Urine β-hCG	A
Blood sample for pharmacogenomics	D
Blood sample for SEP-363856 and SEP-363854 PK	D
Blood sample for antipsychotic levels	D
Urine drug screen	B
Magnetic resonance imaging (MRI) Scan	A
PET/MR Scan including fMRI	E
Positive and Negative Syndrome Scale (PANSS)	A
Clinical Global Impression – Severity (CGI-S)	A
Montgomery-Asberg Depression Rating Scale (MADRS)	A
Columbia Suicide Severity Rating Scale (C-SSRS)	A
Barnes Akathisia Rating Scale (BARS)	A
Abnormal Involuntary Movement Scale (AIMS)	A
Simpson-Angus Scale (SAS)	A
Brief Negative Symptom Scale (BNSS)	A
Adverse events (AEs) monitoring	A
Statistical analysis	SAS®, version 9.1.3 or higher

A = EDC (company name); B = LIMS; C = Core Lab Over-read; D = LIMS/ASCII; E = Computerized Assessment System (Imanova).
Abbreviations: EDC = electronic data capture; CDR = clinical data repository; ePRO = electronic patient reported outcomes; LIMS = laboratory information management system; NA = not applicable; PK = pharmacokinetic.

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 International Council for Harmonization (ICH) Good Clinical Practice (GCP). On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.4. Audits

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

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

16.5. Study Documentation

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

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

16.6. Clinical Laboratory Certification and Normal Values

A local/site laboratory will be used for analysis for most of the clinical laboratory tests for this study. The local/site laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the local/site clinical laboratory selected to analyze 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.

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

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

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

17.2. Institutional Review Board/Independent Ethics Committee

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

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

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

specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

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

17.3. Informed Consent

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval. The Sponsor/CRO may submit informed consent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

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

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

17.4. Subject Privacy

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

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

17.5. Protocol Amendments and Emergency Deviations

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

Emergency deviations or modifications may be initiated without Sponsor, IRB/IEC, or HRA 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, IRB/IEC, and HRA 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. Financial Disclosure

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

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

17.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter

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

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

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19. INVESTIGATOR APPROVAL

I have read the protocol, SEP361-118, Version 5.00 "An Open-Label Positron Emission Tomography Study to Investigate the Effect of Adjunctive Administration of SEP-363856 on Brain Dopamine Synthesis Capacity Using ^{18}F-DOPA 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

ECG equipment and supplies will be provided to the site and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The site 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.
- Indelible ink may be used to mark the placement of the leads on the skin to ensure consistent placement throughout 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, Subjects will be supine for at least 10 minutes prior to and 5 minutes after 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 after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the study center for review and signature.
- The ECG tracing will be kept with subject's source documentation and / or CRF unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the study center.

4. Data Standardization

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

21. APPENDIX II. CLINICAL LABORATORY TESTS

Clinical Safety Panel

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

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), CPK, Creatinine, Glucose, 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: Alcohol test, Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Cotinine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

SEROLOGY PANEL: Hepatitis B Ag, Hepatitis C Ab, HIV-1 Ab, HIV-2 Ab (screening only)

COAGULATION PANEL: International Normalized Ratio (INR), activated Partial Thromboplastin time (aPTT), Prothrombin time (PT)

OTHER TESTS: Serum Pregnancy (β-hCG) (in female subjects only), Urine Pregnancy Test (in female subjects only), follicle stimulating hormone (FSH) (in female subjects only)

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

22. APPENDIX III. 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 upon blood draw, and centrifuge for 20 minutes at ca. x 1300 g to isolate plasma within 30 minutes of blood draw. To ensure a more homogenous sample, all plasma samples should first be transferred to 1 tube, capped and mixed well. Split the harvest plasma sample with approximately equal volume into 2 polypropylene tubes, and label as Primary and Back-up. Freeze plasma tubes in a freezer set at approximately -20°C or lower. The date and clock time of blood collection must be recorded.

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

All samples will be shipped with sufficient dry ice protection.

Study Day	**Collection Time**	**Volume Collected**
Day 1	Pre-dose (approximately 10 minutes prior to dosing)	6 mL
Day 2	2-4 hours Post-dose (Actual date and clock time will be recorded)	6 mL
Day 7	2-4 hours Post-dose (Actual date and clock time will be recorded)	6 mL
Day 14	Prior to PET scan (Actual date and clock time will be recorded)	6 mL
7 days post last day of study drug administration	Actual date and clock time will be recorded	6 mL

23. APPENDIX IV. SAMPLE COLLECTION AND HANDLING GUIDELINES FOR ANTIPSYCHOTIC LEVELS

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

BLOOD SAMPLES FOR ANTIPSYCHOTIC LEVELS

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

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

All samples will be shipped with sufficient dry ice protection.

Study Day	**Collection Time**	**Volume Collected**
-49 to -2	Screening	6 mL
Day -2	Actual date and clock time will be recorded	6 mL
Day 1	Pre-dose (approximately 10 minutes prior to dosing)	6 mL
Day 2	2-4 hours Post-dose (Actual date and clock time will be recorded)	6 mL
Day 7	2-4 hours Post-dose (Actual date and clock time will be recorded)	6 mL
Day 14	Prior to PET scan (Actual date and clock time will be recorded)	6 mL
7 days post last day of study drug	Actual date and clock time will be recorded	6 mL

24. APPENDIX V. SAMPLE COLLECTION AND HANDLING GUIDELINES FOR PHARMACOGENOMICS ASSESSMENT

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

BLOOD SAMPLES FOR PHARMACOGENOMICS

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

25. APPENDIX VI. CYP2D6 INHIBITORS AND SUBSTRATES

The following tables provide examples of CYP2D6 inhibitors (prohibited during participation) and CYP2D6 substrates (concomitant use requires caution) but are not intended to be fully comprehensive lists. Therefore, use of medications for which the potential for interactions mediated by CYP2D6 is in question should be discussed with the medical monitor prior to use.

CYP2D6 Inhibitors

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP2D6	bupropion, fluoxetine, paroxetine, quinidine, terbinafine	cimetidine, cinacalcet, duloxetine, fluvoxamine, mirabegron	abiraterone, amiodarone, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, labetalol, lorcaserin, ritonavir, sertraline, vemurafenib

Reference: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 [accessed 29-May-2019].

CYP2D6 Substrates

	Sensitive Substrates	Moderate Sensitive Substrates
CYP2D6 Substrates	atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine	amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine,

Reference: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1 [accessed 29-May-2019].