SEP-363856

Clinical Study Protocol SEP361-203

A Multicenter Randomized Double-blind followed by an Open-label Extension Study to Evaluate the Efficacy, Safety, and Tolerability of SEP-363856 in Subjects with Parkinson's Disease Psychosis

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician		Telephone: Mobile: Fax: Email:
Medical Monitor		Mobile: Email:
SAE/Pregnancy Reporting		Hotline Number: Fax: Email:

1. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals, Inc.

Name of Investigational Product: SEP-363856

Title of Study: A Multicenter Randomized Double-blind followed by an Open-label Extension Study to Evaluate the Efficacy, Safety, and Tolerability of SEP-363856 in Subjects with Parkinson's Disease Psychosis

Proposed Indication: Parkinson's Disease Psychosis (PDP)

Study Centers: Approximately 24 sites in the United States (US)

Phase of Development: 2

Study Objectives:

Primary:

To evaluate the efficacy of flexibly dosed SEP-363856 (25, 50, or 75 mg/day) in subjects with PDP as measured by the Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD) at Week 6.

Secondary:

Double-blind Period:

- To evaluate the efficacy of SEP-363856 (25, 50, or 75 mg/day) in subjects with Parkinson's Disease Psychosis as measured by:
  - Neuropsychiatric Inventory (NPI)
  - Clinical Global Impression – Severity (CGI-S)
  - Mini Mental State Examination (MMSE) for cognition

Safety:

Double-Blind Period:

- To evaluate the safety and tolerability of SEP-363856 (25, 50, or 75 mg/day) using
  - Adverse event (AE) reports
  - Clinical laboratory results
  - 12-lead electrocardiograms (ECG)
  - Vital signs
  - Physical and neurological examinations (PE, NE)
  - Body weight and body mass index (BMI)
  - Columbia – Suicide Severity Rating Scale (C-SSRS)

Open Label Period:

- To further evaluate the safety and tolerability of open-label flexibly dosed SEP-363856 (25, 50, or 75 mg/day)
  - Adverse event (AE) reports
  - Clinical laboratory results
  - 12-lead electrocardiograms (ECG)
  - Vital signs
  - Physical and neurological examinations (PE, NE)
  - Body weight and body mass index (BMI)

- Columbia – Suicide Severity Rating Scale (C-SSRS)

Other:

Double-blind Period:

- To evaluate the effects of SEP-363856 on sleep quality as measured by the Scales for Outcomes in Parkinson's disease for nighttime sleep quality (SCOPA-NS) and daytime sleepiness (SCOPA-DS).
- To evaluate the effects of SEP-363856 on motor symptoms associated with Parkinson's Disease as measured by the Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and III).
- To evaluate the effects of SEP-363856 on Rapid Eye Movement (REM) Sleep Behavioral Disorder (RBD) symptoms as measured by RBD questionnaire (RBDQ).

Open-label Period:

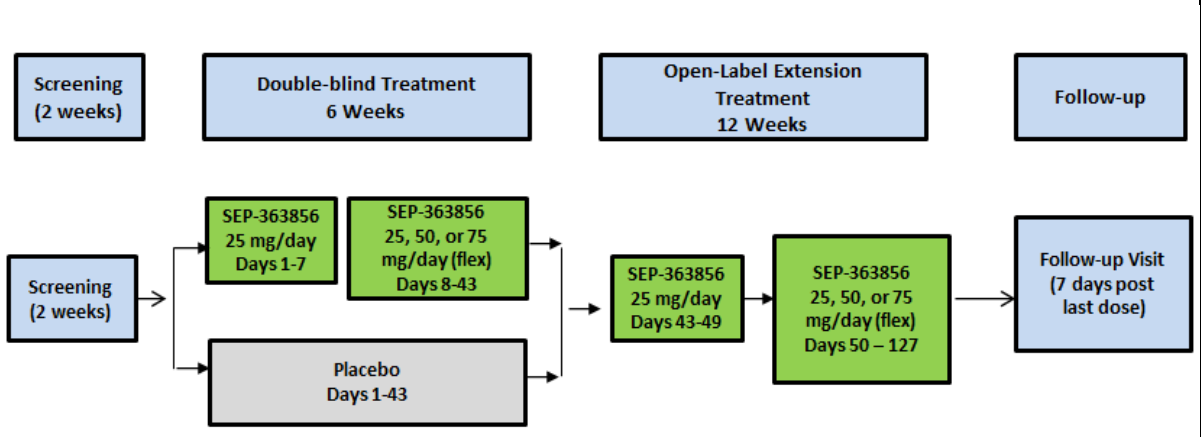
- To further evaluate the effectiveness of flexibly-dosed SEP-363856 over 12-weeks of treatment using:
  - Neuropsychiatric Inventory (NPI)
  - Clinical Global Impression-Severity (CGI-S)
  - Mini Mental State Exam (MMSE)
  - SAPS-PD
- To evaluate the effects of SEP-363856 on sleep quality as measured by the Scales for Outcomes in Parkinson's disease for nighttime sleep quality (SCOPA-NS) and daytime sleepiness (SCOPA-DS).
- To evaluate the effects of SEP-363856 on motor symptoms associated with Parkinson's Disease as measured by the Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and III).
- To evaluate the effects of SEP-363856 on Rapid Eye Movement (REM) Sleep Behavioral Disorder (RBD) symptoms as measured by RBD questionnaire (RBDQ).

Study Design:

This is a multicenter, randomized, parallel-group, placebo-controlled study evaluating the efficacy, safety, and tolerability of double-blind SEP-363856 flexibly dosed at 25, 50, or 75 mg/day for 6 weeks followed by 12 weeks of open-label extension of SEP-363856 flexibly-dosed at 25, 50, or 75 mg/day in male and female subjects ≥ 55 years of age with a clinical diagnosis of PDP. The study will randomize approximately 36 subjects to 2 treatment groups in a 2:1 ratio (approximately 24 subjects to SEP-363856 and 12 to placebo).

The study will consist of 4 periods: Screening/Washout Period (up to 14 days prior to Double-blind Treatment), Double-blind Treatment Period (6 weeks), Open-label SEP-363856 Treatment Period (12 weeks), and Follow-up Period (1 week after last dose) as shown in the following figure. All post-Baseline clinic visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3).

Study Schematic



Note: Double-blind ends with Day 43 assessments; Open-label extension begins Day 43 with first dose in the evening.

Screening/Washout Period (Days -14 to -1):

Subjects who provided written informed consent to participate in the study will be evaluated for eligibility during a screening/washout period of up to 14 days, during which they will be tapered off all antipsychotic or centrally acting anticholinergic medications in a manner that is consistent with labeling recommendations and conventional medical practices. The subject's caregiver must also provide consent for the subject to participate in this study as well as consent for collection of caregiver data as related to the assessment of the subject's neuropsychiatric status measured by the NPI. The screening visit may occur over more than one day. The washout period can start immediately at screening. Prior treatment with antipsychotic agents must be discontinued at least 5 half-lives prior to the site performing the NPI and MMSE screening assessments.

Subjects who meet the study entry criteria at screening (see inclusion criteria in the full protocol in Section 8.1) and have gone through the washout period, as necessary, will enter the 6-week double-blind treatment period.

Double-blind Treatment Period (6 weeks):

Randomization/Treatment:

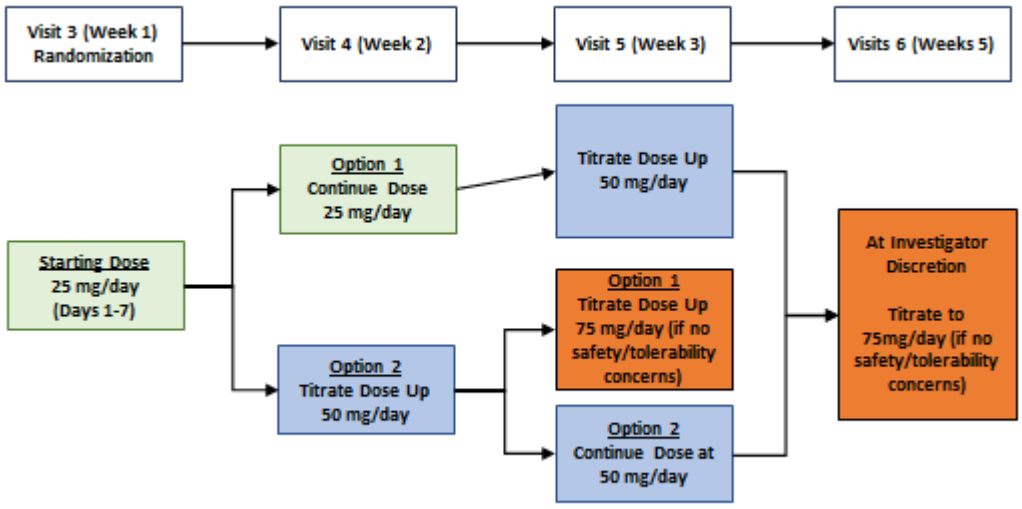
At Baseline (Day 1, Visit 3), subjects who have successfully completed screening/washout will be randomly assigned via interactive voice/web response system (IXRS) in a 2:1 ratio to SEP-363856 or placebo. Study drug dosing will begin following completion of the baseline assessments on the same day (Day 1, Visit 3). Double-blind study drug will be taken in-clinic at the Baseline visit (Day 1) and on visit days when subject titrates up. Subsequent doses starting the following day should be taken at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bedtime. After receiving the initial dose (Day 1) and after each up-titration subjects will remain in the clinic for 2 hours of clinical observation; which will include assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose), additional medical assessments can be performed as needed per investigator discretion. Findings will be collected on appropriate case report forms (CRFs). Subjects will be discharged home if medically stable. Dosing will continue once daily (QD) at bedtime for the remainder of the study, without regard for food.

Subjects will have clinic visits and procedures as outlined in Table 2.Telephone calls to the subjects will be made on the first 2 days after a dose adjustment. An unscheduled visit will be made as early as

possible for dose adjustments or evaluation of safety/tolerability issues. Efforts will be made to ensure that the subject's caregiver remains the same for all study visits. All post-Baseline clinic visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3).

Subjects randomized to SEP-363856 will receive flexible doses of SEP-363856 (25, 50, or 75 mg/day). Subjects will receive SEP-363856 25 mg/day for 1 week (Days 1 - 7). If there are no safety or tolerability issues subjects should be up- titrated to 50 mg/day at Visit 4 (Week 2). Subjects still receiving SEP-363856 25 mg/day must have their dose up- titrated to 50 mg/day at Visit 5 (Week 3), unless approved to stay at 25 mg/day by Medical Monitor due to safety and tolerability concerns. At the investigator's discretion, subject may up -titrate to 75 mg during scheduled visits. During the double-blind period, up-titration will not be allowed after Visit 6 (Week 5). Dose reductions to 50 mg/day or 25 mg/day will be allowed by 1 dose level, at any time for reasons of safety and tolerability. During the double-blind period, following a dose reduction, subjects may increase their dose to the next dose level up to Visit 6 (Week 5) at the Investigator's discretion and only during scheduled visits. If safety or tolerability issues result in study dose discontinuation or reduction, the Investigator must contact the Medical Monitor before the subject is rechallenged. The study medication can be re-introduced if agreed to by the Investigator and Medical Monitor.

Dosing Schematic



Notes:

- Dose reduction is allowed at any time for reasons of safety or tolerability; during unscheduled or scheduled visits.
- During the Double-Blind Period, up-titration to a prior dose level is allowed at Investigator's discretion and only during a scheduled visit.
- At Visit 5 (Week 3), the dose should be up titrated to 50mg/day. In the event of tolerability/safety concerns, the dose may remain at 25 mg/day with Medical Monitor approval.
- Visit 6 (Week 5) is the last visit where up-titration can occur during the Double-Blind Period.

Open-label Extension Period:

For subjects who complete the DB period and continue into the Open-Label (OL) extension, the baseline visit for the open-label period will be the end of double-blind treatment period (Week 6 of DB period). Drug will be taken in-clinic on OL Day 1 (Study Day 43) of the open-label period and on

study visit days when subject up-titrates; with subsequent dosing starting the following day at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bedtime. After receiving the initial dose of 25 mg (OL Day 1) and after each up-titration, subjects will remain in the clinic for 2 hours of clinical observation; which include assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion. Findings will be collected on appropriate case report forms (CRFs). Subjects will be discharged home if medically stable. Dosing will continue once daily (QD) at bedtime for the remainder of the study, without regard for food.

The total daily dose will remain between 25 mg/day and 75 mg/day for the 12-week treatment period. Subjects will receive SEP-363856 25 mg/day for 1 week. If there are no safety or tolerability issues, subjects should be up-titrated to 50 mg/day at Visit 8 (OL Week 2; OL Day 8). Subjects still receiving SEP-363856 25 mg/day should have their dose up- titrated to 50 mg/day at Visit 9 (OL Week 3), however may remain at 25 mg/day due to safety/tolerability issues with medical monitor approval. At the investigator's discretion, subject may up-titrate to 75 mg during scheduled visits.

Dose reductions will be allowed by 1 dose level, at any time for reasons of safety and tolerability. Following a dose reduction, subjects may increase their dose at the Investigator's discretion and only during scheduled visits. If safety or tolerability issues result in study medication dose discontinuation or reduction, the Investigator must contact the medical monitor before the subject is re-challenged. The study medication can be re-introduced if agreed to by the Investigator and Medical Monitor.

A minimum of 7 days is required between dose increases. Dose decreases may be made at any time, at the Investigator's discretion, for reasons of safety or tolerability. If, in the judgment of the investigator, the subject does not tolerate the minimum required dose (25 mg/day), the subject will be discontinued from the study.

During the OL treatment period, subjects will return to the clinic and have assessments as described in Table 3.

Telephone calls to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease). At Study Week 12 and Study Week 16 (midpoint between Visit 11 and Visit 12, and midpoint between Visit 12 and Visit 13) the site staff will contact the subject via telephone in order to monitor for AEs, SAEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration, and upcoming visits. If necessary, an unscheduled visit will be made as early as possible for dose adjustments or evaluation of safety/tolerability issues.

Follow-up Period (7 days):

All subjects who either complete the Treatment Period or discontinue early will have a Follow-up Visit for final safety assessments 7 days (± 2 days) after the last dose of study drug.

Study Assessments

Double Blind Period:

Efficacy will be assessed by the SAPS-PD, the NPI, CGI-S, and the MMSE. Safety and tolerability will be monitored throughout the study by collection of AEs, clinical laboratory parameters, ECGs, vital signs, PE and NE, C-SSRS, body weight, and BMI. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation.

The quality of nighttime sleep as well as daytime sleepiness will be assessed by the SCOPA-NS and the SCOPA-DS, respectively. The effects of SEP-363856 on motor symptoms will be assessed by the UPDRS II and III, and its effects on REM behavioral disorder assessed by the RBDQ.

Blood samples for the determination of SEP-363856 and SEP-363854 plasma concentrations will be collected as described in Table 2. Population pharmacokinetic (POPPK) analyses will be performed utilizing the data, results of which will be provided in a separate report.

OL Extension Period:

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

Efficacy will be assessed by the NPI, the CGI-S, and the MMSE.

The quality of nighttime sleep as well as daytime sleepiness will be assessed by the SCOPA-NS and the SCOPA-DS, respectively. The effects of SEP-363856 on motor symptoms will be assessed by the UPDRS II and III, and its effects on REM behavioral disorder assessed by the RBDQ.

Blood samples for the determination of SEP-363856 and SEP-363854 plasma concentrations will be collected as described in Table 3. Population pharmacokinetic (POPPK) analyses will be performed utilizing the data, results of which will be provided in a separate report.

Diagnosis and Main Criteria for Subject Inclusion:

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

Inclusion criteria (not all inclusive):

- Subject, caregiver, and/or legally authorized representative understands and is willing to sign informed consent to participate in the study.
- Subject must be willing and able to comply with the study procedures and visit schedules and must be able to follow verbal and written instructions.
- Subject is male or postmenopausal female ≥ 55 years of age.
- Subject meets established diagnostic criteria for Parkinson's disease of at least one year duration, consistent with the UK Brain Bank criteria.
- Subject has psychotic symptoms that began after the diagnosis of PD for at least one month, occurring at least weekly in the month prior to screening (according to subject or caregiver report), and severe enough to warrant treatment with antipsychotics.
- Subject has a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI) Item A (delusions) and/or Item B (hallucinations). This criterion must be met at Visit 1 and Visit 3.
- Subject has a Mini Mental State Examination (MMSE) score > 16 points out of 30.

- Subject has a caregiver (eg, spouse or family member) who will be required to attend all visits and is able to provide study information on various scales such as the NPI.
- Subject is taking antiparkinsonian drugs or deep brain stimulation, with a stable dose/dose regimen and settings for 1 month before screening.

Exclusion Criteria (not all inclusive):

- Subject has psychosis secondary to other toxic or metabolic disorders.
- Subject has dementia diagnosed concurrent with or before Parkinson's disease, motor symptoms that began less than one year before the onset of dementia or symptoms consistent with the diagnosis of Lewy Body Dementia (DLB) or if the psychosis occurred after ablative stereotaxic surgery.
- Subject has had a stroke or other uncontrolled serious medical or neurological illness within 6 months of baseline.
- Subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS at Screening (ie, in the past one month) or baseline (ie, since last visit).
- Subject has participated in an investigational drug study and received investigational drug within 30 days (or longer if the half-life is known to be ≥ 150 hours) prior to the screening visit, or who is currently participating in another interventional study. Observational studies are not exclusionary. Subject has previously received SEP-363856.

Randomization Criteria

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

- Subject must have a combined score of at least 6 or an individual score of at least 4 on the Neuropsychiatric Inventory (NPI) Item A (delusions) and/or Item B (hallucinations) at Baseline (Day 1).
- Subject must continue to meet all other inclusion criteria and none of the exclusion criteria at Baseline (Day 1).

Continuation into Open-label Extension Criteria

To qualify for continuation into the open-label extension period, subjects must meet the following criteria:

- Subject must have completed the 6-week double-blind treatment period.
- Subject has not taken any medication other than the study drug for the purpose of controlling PDD symptoms.
- There has been no clinically significant change in the subject's medical condition or Parkinson's disease, in the opinion of the investigator.
- Subject has not answered "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at any time during the DB treatment period.

Investigational Product, Dosage and Mode of Administration: SEP-363856 treatment will be size #0, Swedish-orange capsules (25 mg, 50 mg or 75 mg) administered orally once daily (QD). Study drug may be taken without regard for food at approximately the same time each evening before bedtime. During the double-blind treatment period all subjects randomized to SEP-363856 will be flexibly dosed at 25, 50, or 75 mg/day. During the open-label treatment period all subjects will receive SEP-363856 flexibly dosed at 25, 50 or 75 mg/day.
Duration of Treatment: 6 weeks for DB period, 12 weeks for open-label
Reference Therapy, Dosage and Mode of Administration: During the double-blind treatment period, matching placebo size #0, Swedish-orange capsules administered orally once daily. Study drug may be taken without regard for food at approximately the same time each evening before bedtime. Subjects randomized to placebo will receive placebo during the double-blind treatment period.
Concomitant Medications: Subjects taking nonpsychotropic medications must be on a stable dose within 30 days prior to screening, and maintain the dose and regimen throughout the study. Subjects must maintain their anti-Parkinson's medications on a stable dose throughout the study. Dose adjustments must be approved by the medical monitor. Prior treatment with antipsychotic agents (including pimavanserin) must be discontinued at least 5 half-lives prior to randomization. Prior treatment with centrally acting anticholinergic agents including but not limited to diphenhydramine, trihexyphenidyl, and biperidin must be discontinued no less than two weeks prior to randomization. Antipsychotic and centrally acting anticholinergic medications are prohibited during the course of the study. Use of antidepressant, anxiolytic, and sleep medications is allowed. The dose of these medications must be a stable dose within 30 days prior to screening and be maintained throughout the study. Medications for the treatment of anxiety/agitation such as lorezapam up to a dose of 6 mg/day or its equivalent are permitted with prior authorization from the Medical Monitor and should not be used within 8 hours prior to efficacy assessments. See Section 10.3 of full protocol for full description of concomitant medications and restrictions.

Study Endpoints:

Primary Endpoint:

The primary endpoint is the change from double-blind Baseline in total SAPS-PD score at Week 6.

Secondary Endpoints:

Double Blind Period:

- Change from DB Baseline in the CGI-S at Week 6.
- Change from DB Baseline in NPI at Week 6.
- Change from DB Baseline in MMSE at Week 6.

Safety Endpoints:

Double Blind Period:

- The incidence of AEs, serious adverse events (SAEs), and AEs (or SAEs) leading to discontinuation during the double-blind period.
- Absolute values and changes from Baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], and 12-lead ECGs).
- Frequency of subjects with suicidal ideation or suicidal behavior using the C-SSRS during the double-blind period.

Open-label Period:

- The incidence of AEs, serious adverse events (SAEs), and AEs (or SAEs) leading to discontinuation during the open-label extension and overall.
- Absolute values and changes from DB and OL Baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], and 12-lead ECGs).
- Frequency of subjects with suicidal ideation or suicidal behavior using the C-SSRS during the open-label extension and overall.

Other Endpoints:

Double Blind Period:

- Change from DB Baseline in nighttime sleep quality as measured by the SCOPA-NS at Week 6.
- Change from DB Baseline in daytime sleepiness as measured by the SCOPA-DS at Week 6.
- Change from DB Baseline in the UPDRS II and III at Week 6.
- Change from DB baseline in RBD symptoms at Week 6 as measured by the RBDQ.

Open Label Period:

- Change from DB and OL Baseline in nighttime sleep quality as measured by the SCOPA-NS at Week 18.
- Change from DB and OL Baseline in daytime sleepiness as measured by the SCOPA-DS at Week 18.

- Change from DB and OL Baseline in the UPDRS II and III at Week 18.
- Change from DB and OL baseline in RBD symptoms as measured by the RBDQ at Week 18.
- Change from DB and OL Baseline in the CGI-S at Week 18.
- Change from DB and OL Baseline in NPI at Week 18.
- Change from DB and OL Baseline in MMSE at Week 18.
- Change from DB and OL Baseline in total SAPS-PD at Week 18.

Statistical Methods:

The analysis of efficacy will be based on the modified Intent-to-Treat (mITT) population, which includes all subjects who are randomized, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline efficacy measurement. The analysis of safety assessments will use the Safety population, which includes all subjects who are randomized and have received at least one dose of study drug.

The primary efficacy variable is the change from baseline in SAPS-PD score at Week 6 during the DB period for testing superiority of SEP-363856 to placebo. A Mixed Model for Repeated Measures (MMRM) will be used for this comparison. The MMRM model will include factors for treatment, visit (as a categorical variable), and treatment-by-visit interaction, and include baseline SAPS-PD score as a covariate. An unstructured covariance matrix will be used for the within-subject correlation and the Kenward-Rogers approximation will be used to calculate the denominator degree of freedom.

The secondary efficacy variables including change from baseline in CGI-S scores at Week 6, as well as change from baseline in NPI score and MMSE at Week 6 and will be analyzed similarly.

Descriptive statistics of observed values and changes from DB baseline and OL baseline in SAPS-PD, CGI-S score, NPI total score, MMSE total score, SCOPA-NS and SCOPA-DS total scores, and RBDQ total score will be summarized by visit.

Safety data including AEs, laboratory values, clinical evaluations, and C-SSRS will be summarized by treatment group overall and by study period (DB treatment period, open-label extension period). Adverse events, AEs leading to discontinuation, and serious AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects with any AE, and AEs by system organ class and preferred term. Adverse events will be further summarized by severity and by relationship to study drug. The summary of AEs will include any AE occurring on or after the first dose of study drug.

Sample Size:

A total of approximately 36 subjects will be randomized in 2:1 ratio to SEP-363856 and placebo, with approximately 24 subjects assigned to SEP-363856 and 12 subjects assigned to placebo. The sample size will provide powers of 59%, 48%, 37%, and 27% to detect treatment effect sizes of 0.8, 0.7, 0.6, and 0.5, respectively, in change from Baseline in SAPS-PD at Week 6 for SEP-363856 versus placebo. It was estimated by using a two independent sample t-test method with 2-sided significant level of 0.05. The sample size was determined for the purposes of exploring the efficacy, safety and tolerability of flexible dosing with SEP-363856 (25, 50, or 75 mg/day) for 6 weeks in male and female subjects with a clinical diagnosis of PDP. A sufficient number of subjects will be enrolled to ensure 36 randomized subjects.

Table 2 Schedule of Assessments – Double Blind Period

	Screen/ Washout	Double-blind Treatment				
Study Visit Number	**Visit 1**	**Visit 3[a]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ OL Baseline**
Study Visit Week[a]	**-2**	**1**	**2**	**3**	**5**	**6**
Study Visit Day	**-14 to -1**	**1**	**8 (± 2 d)**	**15 (± 2 d)**	**29 (± 2 d)**	**43 (± 2 d)**
Obtain informed consent (subject and caregiver)	X					
Review inclusion/exclusion criteria	X	X				
Review Continuation Criteria for Open-label Extension						X
Review randomization criteria		X				
Prior/concomitant medication review	X	X	X	X	X	X
Randomize (IXRS) to treatment		X				
Dispense study drug[c]		X	X	X	X	X
Study drug accountability			X	X	X	X
Telephone contacts	A telephone call to the subject will be made on the first 2 days after initial dosing of DB and OL study drug (Day 1 and Day 43) and after any dose adjustment (increase or decrease) is made.[d]					
Clinical and Laboratory Evaluations						
Demography	X					
Medical history	X					
Psychiatric history/mental status	X					
Physical and neurological examination	X	X				X
Height	X					
Vital signs[e]	X	X	X	X	X	X
Weight[l]	X	X				X
Electrocardiogram (ECG)	X	X				X

Table 2: Schedule of Assessments – Double Blind Period (Continued)

	Screen/ Washout	Double-blind Treatment				
Study Visit Number	**Visit 1**	**Visit 3[a]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ OL Baseline**
Study Visit Week[a]	**-2**	**1**	**2**	**3**	**5**	**6**
Study Visit Day	**-14 to -1**	**1**	**8 (± 2 d)**	**15 (± 2 d)**	**29 (± 2 d)**	**43 (± 2 d)**
Hematology, chemistry, and urinalysis	X	X				X
Serum prolactin[k]	X	X				X
Serum or plasma glycosylated hemoglobin (HbA_{1c})	X	X				X
Serum or plasma glucose and lipid panel	X	X				X
Thyroid panel (TSH)	X					
Coagulation panel (PTT, aPTT, INR)	X					
Serum follicle stimulating hormone (FSH), females only[f]	X					
Serum human chorionic gonadotropin (β-hCG), females only[g]	X					
Breath alcohol test		X				X
Informed consent and blood sample for pharmacogenomics (CYPP450 2D6)		X				
Blood sample for plasma SEP-363856 PK[h]		X				X
Urine drug screen[i]	X					X
Scale for Assessment of Positive Symptoms (SAPS-PD)		X	X	X	X	X
Neuropsychiatric Inventory (NPI)	X	X		X		X
Clinical Global Impression – Severity (CGI-S)		X		X		X
Mini Mental State Exam (MMSE)	X	X		X		X
Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and III)		X	X	X	X	X

Table 2: Schedule of Assessments – Double Blind Period (Continued)

	Screen/ Washout	Double-blind Treatment				
Study Visit Number	**Visit 1**	**Visit 3[a]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ OL Baseline**
Study Visit Week[a]	**-2**	**1**	**2**	**3**	**5**	**6**
Study Visit Day	**-14 to -1**	**1**	**8 (± 2 d)**	**15 (± 2 d)**	**29 (± 2 d)**	**43 (± 2 d)**
Scales for Outcomes in Parkinson's Disease Sleep Scale – Daytime Sleepiness (SCOPA-DS)		X		X		X
Scales for Outcomes in Parkinson's Disease Sleep Scale – Nighttime Sleep Quality (SCOPA-NS)		X		X		X
Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire (RBDQ)		X		X		X
Columbia Suicide Severity Rating Scale (C-SSRS)[i]	X	X	X	X	X	X
Pretreatment event and Adverse events (AE) monitoring	X	X	X	X	X	X

Note: Footnotes appear under Table 3

Table 3: Schedule of Assessments – Open-Label Period

	Open-Label Treatment						
Study Visit Number	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13/ EOT/ET**	**Visit 14 Follow-up**
Study Visit Week[a] (Open-label Week)	**Week 7 (OL Wk 1)**	**Week 8 (OL Wk 2)**	**Week 9 (OL Wk 3)**	**Week 10 (OL Wk 4)**	**Week 14 (OL Wk 8)**	**Week 18 (OL Wk 12)**	**7 days post last dose (± 2 days)**
Study Visit Day (OL Study Day)	**Day 50 ± 2 (OL Day 8)**	**Day 57 ± 2 (OL Day 15)**	**Day 64 ± 2 (OL Day 22)**	**Day 71 ± 3 (OL Day 29)**	**Day 99± 3 (OL Day 57)**	**Day 127 ± 3 (OL Day 85)**	
Concomitant Medications review	X	X	X	X	X	X	X
Dispense Study Drug[c]	X	X	X	X	X		
Study Drug Accountability	X	X	X	X	X	X	
Telephone contacts[d]	A telephone call to the subject will be made on the first 2 days after a dose adjustment (increase or decrease) as well as at Study Week 12 and Week 16 (midpoint between Visit 11 and Visit 12, and midpoint between Visit 12 and Visit 13)[d]						
Physical Examination and neurological examination				X		X	X
Vital Sign Measurements[e]	X	X	X	X	X	X	X
Weight[l]				X		X	X
12-Lead Electrocardiogram (ECG)				X		X	
Hematology, Chemistry, and Urinalysis				X		X	
Serum prolactin[k]				X		X	
Blood sample for plasma SEP-363856 PK[h]				X		X	
Serum or plasma glycosylated hemoglobin (HbA_{1c})				X		X	
Serum or plasma glucose and lipid panel				X		X	
Breath alcohol text				X		X	
Urine drug screen[i]				X		X	
Neuropsychiatric Inventory (NPI)	X[m]			X	X	X	
Scale for Assessment of Positive Symptoms (SAPS-PD)				X	X	X	
Clinical Global Impressions of Severity (CGI-S)	X			X	X	X	
Mini Mental State Exam (MMSE)	X[m]			X	X	X	
Unified Parkinson's Disease Rating scale Parts 2 and 3 (UPDRS II and III)	X	X	X	X	X	X	

Table 3: Schedule of Assessments – Open-Label Period (Continued)

	Open-Label Treatment						
Study Visit Number	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13/ EOT/ET**	**Visit 14 Follow-up**
Study Visit Week[a] (Open-label Week)	**Week 7 (OL Wk 1)**	**Week 8 (OL Wk 2)**	**Week 9 (OL Wk 3)**	**Week 10 (OL Wk 4)**	**Week 14 (OL Wk 8)**	**Week 18 (OL Wk 12)**	**7 days post last dose (± 2 days)**
Study Visit Day (OL Study Day)	**Day 50 ± 2 (OL Day 8)**	**Day 57 ± 2 (OL Day 15)**	**Day 64 ± 2 (OL Day 22)**	**Day 71 ± 3 (OL Day 29)**	**Day 99± 3 (OL Day 57)**	**Day 127 ± 3 (OL Day 85)**	
Scales for Outcomes in Parkinson's Disease Sleep Scale – Daytime Sleepiness (SCOPA-DS)				X		X	
Scales for Outcomes in Parkinson's Disease Sleep Scale – Nighttime Sleep Quality (SCOPA-NS)				X		X	
Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire (RBDQ)				X		X	
Columbia – Suicide Severity Rating Scale (C-SSRS)[j]	X	X	X	X	X	X	X
Adverse Event monitoring	X	X	X	X	X	X	X

Abbreviations: aPTT = activated partial thromboplastin time; BSN = baseline; d = day; EOS = End of Study; EOT = End of Treatment; ET = early termination; INR = International Normalized Ratio; IXRS = interactive voice/web response system; OL = open-label; PK = Pharmacokinetics; PTT = partial thromboplastin time; V = visit.

[a] Visit numbering 2 intentionally skipped. Days 1, 8, 15, and 29 are the first days of Weeks 1, 2, 3, and 5, respectively. The Day 43 visit occurs the day after last dose at the end of Week 6. For Visits 8 through 13 the study days occur at the end of the Visit Week.

[b] (no footnote b) Letter intentionally skipped.

[c] Study drug dosing will be taken in-clinic at Visit 3 (Day 1) and Visit 7 (Day 43; OL Day 1), and on visit days when subject titrates up; with subsequent doses starting the following day at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bedtime. Study drug will be taken without regard for food.

[d] If subject appears to be symptomatic as assessed by the site during a telephone contact and requires additional assessments in-clinic, an unscheduled visit will be made as early as possible. See Section 11.9.12 for procedures and assessments for unscheduled visits.

[e] Vital signs will include sitting and standing measurements of blood pressure and heart rate, respiratory rate, and oral body temperature. All clinic visits will have predose vitals. Visit 3 (Day 1) and Visit 7 (OL Day 1) and any clinic visit that a subject titrates up, vitals will also be collected 1 (± 15 min) hour and 2 hours (± 15 min) post dose, additional medical assessments can be performed as needed per investigators discretion.

[f] If female, blood samples for follicle stimulating hormone (FSH) will be collected.

[g] If female, blood sample will be collected for β-hCG test.

[h] Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected predose (before study drug administration) and between 1-3 hours post dose on Day 1. One sample will be collected on Day 43 (12 ± 4 hours after the Day 42 dose), Day 71 (OL Day 29) (12 ± 4 hours after the Day 70 [OL Day 28] dose), and Day 127 (OL Day 85) (12 ± 4 hours after the Day 126 [OL Day 84] dose). The time and date of the 3 previous doses of study drug, time, and date of sampling must be recorded. The time and date of food intake will be recorded on Day 43 when blood samples are collected for determination of plasma SEP-363856 concentrations.

[i] Urine drug screen may be ordered at other visits as deemed clinically appropriate. These results should be discussed with the Medical Monitor.
[j] C-SSRS Baseline/Screening version will be administered for Visit 1; all other visits will administer the C-SSRS Since Last Visit version.
[k] Post Screening Serum prolactin results will remain blinded.
[l] BMI will be calculated by site staff using an equation for BMI at Screening only. BMI for all other visits will be derived within the Electronic Data Capture (EDC) system.
[m] Screening assessments must be performed after washout.
NOTE: Subjects will remain at the clinical site on Day 1 and Visit 7 (Day 43; OL Day 1) until the Investigator deems it appropriate to discharge the subject.
NOTE: Efforts will be made to ensure that the subject's caregiver remains the same for all study visits.
NOTE: All double-blind post-Baseline visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3). OL study day is based on days from the OL baseline Visit 7.
NOTE: For this study 1 week is defined as 7 days and 1 month is defined as 4 weeks (28 days).
NOTE: The SAPS-PD, CGI-S, MMSE, UPDRS II, UPDRS III, and neurological exam should be performed during the subject's on-periods (ie, at a time when the subject shows no clinical evidence of worsening in their Parkinson's symptoms, as determined by the site investigator). The NPI is administered to the caregiver only and should be completed referencing the subject's on-period.

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are provided in Table 4 and Table 5.

Table 4: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
β-hCG	Serum human chorionic gonadotropin
BMI	Body mass index
BOLD	Blood oxygen level dependent
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CDR	Clinical data repository
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome
DA	Dopamine
ECG	Electrocardiogram
EDC	Electronic data capture
EEG	Electroencephalogram

Table 4: List of Abbreviations (Continued)

Abbreviation	Full Form
ET	Early termination
FDA	US Food and Drug Administration
fMRI	functional magnetic resonance imaging
FSH	Serum follicle stimulating hormone
GCP	Good Clinical Practice
5-HT	5-hydroxytryptamine (serotonin)
HbA_{1c}	Serum or plasma glycosylated hemoglobin
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPD	Important protocol deviation
IRB	Institutional Review Board
IXRS	Interactive voice/web response system
LOCF	Last observation carried forward
LIMS	Laboratory information management system
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MID	Monetary incentive delay
mITT	Modified Intention-to-Treat
MMRM	Mixed Model for Repeated Measures
MMSE	Mini Mental State Examination
MTD	Maximum tolerated dose
N2	NREM sleep stage 2
N3	NREM sleep stage 3
NCS	Not clinically significant
NE	Neurological examination
NPI	Neuropsychiatric Inventory
NREM	Non-rapid eye movement sleep
OL	Open-label
PD	Parkinson’s disease

Table 4: List of Abbreviations (Continued)

Abbreviation	Full Form
PDP	Parkinson's disease psychosis
PE	Physical examination
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
POPPK	Population pharmacokinetics
PR	Time between P wave and QRS in electrocardiography
PSG	Polysomnography
PT	Preferred term
PTT	Partial thromboplastin time
PVG	Pharmacovigilance
QD	Once daily
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RBD	Rapid Eye Movement (REM) Sleep Behavioral Disorder
RBDQ	Rapid Eye Movement Sleep Behavior Disorder Questionnaire
REM	Rapid eye movement
RR	Respiration rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAPS	Scale for Assessment of Positive Symptoms
SAPS-PD	Scale for Assessment of Positive Symptoms – Parkinson's Disease
SCOPA-DS	Scales for Outcomes in Parkinson's Disease Sleep Scale – Daytime Sleepiness
SCOPA-NS	Scales for Outcomes in Parkinson's Disease Sleep Scale – Nighttime Sleep Quality
SOC	System organ class
TAAR1	trace amine associated 1 receptors
US, USA	United States, United States of America

Table 4: List of Abbreviations (Continued)

UPDRS	Unified Parkinson's Disease Rating scale
USP	United States Pharmacopeia
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
YOPD	Young onset Parkinson's disease

Table 5: 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.
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) or Investigational Product	Term to cover investigational drug and placebo.
Treatment Period	The period of the study in which the double-blind study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and was assigned a randomization number.
Enrolled Subject	Any subject who was successfully screened and enrolled into the pre-randomization period of the study.
Randomization Failures	Any subject who was enrolled but not randomized.
Completed Subject	Any subject who completed the study by participating throughout the duration of the study, up to and including the last in-clinic visit.
Early Termination Subject	Any subject who was successfully screened and randomized into the treatment period of the study, but did not complete the study.
End of Treatment	The day that the subject receives protocol-defined last dose of the study drug. This may or may not include a taper period.
End of Study	The day that the subject completes the study per the study design.
1 Week	Defined as 7 days.
1 Month	Defined as 28 days.
On-Period	Defined as a time when the subject shows no clinical evidence of worsening in their Parkinson's symptoms, as determined by the site investigator.

4. INTRODUCTION

4.1. Background

Parkinson's disease (PD) is a chronic neurodegenerative disorder that affects motor control. It is the second most common neurodegenerative disease after Alzheimer's disease and affects approximately 1 million people in the United States (US) and 7 million people globally. The mean age of onset is around 60 years, although 5 to 10% of cases, classified as young onset PD (YOPD), begin between the ages of 20 and 50. The main pathological characteristic of PD is neuronal cell death in the substantia nigra, which leads to loss of dopamine, a critical neurotransmitter involved in movement control. PD has been increasingly recognized as having a multitude of non-motor symptoms including psychosis, cognitive impairment, and dementia mood disturbances, fatigue, apathy, and sleep disorders.

Parkinson's disease psychosis (PDP) is a common and debilitating condition. Symptoms commonly include visual hallucinations, delusions (paranoia) and illusions (misperception of objects). Estimates on the incidence of PDP vary widely depending on the study from 40% (Fénelon-2000, Chou-2005) to as high as 60% (Fénelon-2010 and Riedel-2010). The risk for PDP increases with disease duration and severity, as well as with declines in cognitive function, increased age, depression, and sleep disorders (Papapetropoulous-2005). PDP has also been associated with poorer quality of life, increased morbidity and mortality in addition to increased caregiver burden and nursing home placement (Aarsland-2000). Underlying pathogenesis remains uncertain although psychotic symptoms are likely attributable in part to the effects of dopamine agonists used in the treatment of PD. Dopaminergic agonists can stimulate limbic dopamine D2 receptors to produce psychotic symptoms, in much the same way as in schizophrenia. Although lowering the dose of dopamine agonists can alleviate the symptoms of PDP, they can also worsen the motor symptoms associated with PD. Disturbances in 5-HT (5-hydroxytryptamine [serotonin]), including 5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C} receptors, may also contribute to PDP as well other behavioral disorders associated with PD such as depression and anxiety (Ballanger-2010).

Treatment of psychosis involves the use of typical or atypical antipsychotic medications, which act predominantly as dopamine D_2 receptor antagonists. For PDP, such pharmacological treatment is fraught with risk as D_2 antagonism may also target the symptomatic dopamine (DA) replacement therapy used in PD and potentially worsen motor symptoms. In addition antipsychotics carry a boxed warning against their use in elderly patients with psychosis due to increased mortality and morbidity (Friedman-2010). Two agents commonly used to treat PDP are clozapine and quetiapine as off-label use.

Clozapine has higher affinity for serotonin 5-HT_{2A} receptors than for D_2 receptors. Low-dose clozapine ($\leq$ 50 mg) has been demonstrated as an effective treatment (The Parkinson Study Group-1999); the dose levels used in PDP are significantly lower than the therapeutic dose used for the treatment of schizophrenia (300 - 900 mg). The use of low-dose clozapine in PDP, however, is limited by its adverse effects, in particular, agranulocytosis, which is not dose related (Thomas-2010).

Quetiapine is an atypical antipsychotic, similar in structure to clozapine. It exhibits strong antagonism of $5HT_2$ receptors and weak antagonism of D_2 receptors. The American Academy of

Neurology's task force on PD treatment recommends quetiapine as a treatment option after clozapine has been considered. The use of low-dose quetiapine in PDP is also limited by its adverse effects, in particular, sedation and metabolic changes including hyperglycemia, dyslipidemia and weight gain.

Nuplazid™ (pimavanserin), a selective 5-HT_{2A} inverse agonist, is the first treatment approved for PDP indication by the US Food and Drug Administration (FDA) in April 2016. A recently completed clinical study investigating the use of pimavanserin in subjects with PDP demonstrated significant improvements in the primary endpoint as measured by the SAPS-PD (Scale for Assessment of Positive Symptoms – Parkinson's Disease) and in several secondary and exploratory outcomes, including the Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression – Severity (CGI-S), night-time sleep, daytime wakefulness and caregiver burden (Cummings-2014). Pimavanserin was well-tolerated; however, there was an imbalance of serious adverse events including death in the pimavanserin group compared to the placebo group although no particular (serious adverse event) SAE was more prominent than others. In addition, pharmacokinetic (PK) studies showed that pimavanserin did not reach steady-state plasma levels until after 10 to 14 days of repeated daily administration in PD patients (Hacksell-2014) while improvement in psychotic symptoms was not observed until 2 to 3 weeks after initiation of treatment (Cummings-2014).

Effective agents for PDP are scarce and serious adverse side effects associated with their use are limiting. Although pimavanserin appears to be a promising agent, concerns remain for its modest efficacy, safety and its delay in onset of action, which together may limit its use. The development of effective and well-tolerated treatments for patients with PDP is therefore warranted.

4.2. Study Conduct Rationale

SEP-363856 is a central nervous system (CNS) active drug, which shows broad efficacy in animal models of schizophrenia (positive and negative symptoms) and depression. The molecular target responsible for this profile of effects has not been completely elucidated, but may include actions at 5-HT1A and trace amine-associated 1 (TAAR1) receptors. Rat electroencephalogram (EEG) studies showed that SEP-363856 dose dependently suppressed rapid eye movement (REM) sleep. In nonhuman primate functional magnetic resonance imaging (fMRI) experiments, pretreatment with SEP-363856 reduces the ketamine brain fMRI response in rhesus monkey in a pattern analogous to that observed with risperidone, supporting an antipsychotic-like profile. Together these data revealed that SEP-363856 exhibits clear, functional CNS pharmacodynamic signals in rats and nonhuman primates. Importantly, SEP-363856 was not shown to cause Parkinson's symptoms (eg, catalepsy) in preclinical models.

As of 24 September 2018, a total of 246 subjects have received SEP-363856 in 8 completed Phase 1 clinical studies (SEP361-101, SEP361-103, SEP361-104, SEP361-105, SEP361-106, SEP361-108, SEP361-111, and DA801002). An additional 199 subjects received oral doses of SEP-363856 in studies in adults with schizophrenia: Phase 2 Study SEP361-201 (safety, tolerability, and efficacy in adult subjects diagnosed with schizophrenia; clinical study report is pending), Phase 2 Study SEP361-202 (long-term safety and maintenance of effect in subjects

diagnosed with schizophrenia and Phase 1 Study DA801004 (safety, tolerability, multiple ascending dose PK, in Japanese subjects diagnosed with schizophrenia).

Evidence for target engagement and pharmacodynamic effects were demonstrated in the following studies.

- Study SEP361-103 was a randomized, double-blind, placebo-controlled, crossover polysomnography (PSG) study that investigated the effect of a single oral dose (50 mg and 10 mg) of SEP-363856 on REM sleep suppression in healthy adult male subjects. A single 50 mg oral dose of SEP-363856 suppressed REM sleep in all subjects (increased latency to REM sleep and reduced time spent in REM sleep) and increased non-rapid eye movement sleep (NREM) sleep stage 2 (N2), and NREM sleep stage 3 (N3) (deep or slow wave sleep). A single 10 mg dose of SEP-363856 also increased latency to REM sleep to a lesser extent, but did not reduce time spent in REM sleep.
- Study SEP361-104 was a randomized, double-blind, placebo-controlled, single dose study of the effects of SEP-363856 (50 mg) and amisulpride (400 mg) on blood oxygen level dependent (BOLD)-fMRI signals in healthy male and female adult subjects with high or low schizotype characteristics. FMRI was used in combination with the monetary incentive delay (MID) task to examine the single dose effects of SEP-363856 on changes in reward processing. During the anticipation/motivational phase of the MID task, SEP-363856 modulated striatum, insula and orbitofrontal cortex brain activity, similar to the fMRI effects observed with the D2 antagonist amisulpride.
- Study SEP361-106 (Part 2) was an open-label study that investigated the PK and efficacy of SEP-363856 75 mg given QD for 28 days to 16 male and female subjects with schizophrenia. Treatment demonstrated improvement in efficacy (PANSS total score, CGI-S) compared with Baseline. Furthermore, ad hoc subgroup analyses showed a significantly greater decrease from Baseline in PANSS total scores at the end of the 28-day treatment period in subjects who had less frequent hospitalizations per year of illness compared with subjects who had more frequent hospitalizations per year of illness.
- Study SEP361-108 evaluated the effects of SEP-363856 25 and 50 mg given QD for 14 days compared with placebo in 15 adult male and female subjects with narcolepsy-cataplexy. The frequency of cataplexy attacks and overall narcolepsy symptoms were assessed by the CGI-I scale. The primary objective of the study was not met, as SEP-363856 did not demonstrate separation from placebo at either dose studied (25 and 50 mg QD) for the primary endpoints (total number of cataplexy attacks and CGI-I) at the end of the 2 week treatment period. However, SEP-363856 did demonstrate suppression of REM in narcoleptic subjects (Night 1 data), which was maintained with repeated dosing (Day 14 effect on sleep onset REM periods). These data demonstrate that central activity was observed at both doses studied (25 and 50 mg QD).

Overall, across all clinical studies conducted as of 24 September 2018, SEP-363856 has been generally well-tolerated. The majority of adverse events (AEs) observed to date have been mild

to moderate in severity and non-serious. One death due to acute cardiovascular insufficiency was reported in the SEP-363856 group in Study SEP361-201; final autopsy results identified significant chronic coronary heart disease as contributing to the cause of death. Treatment-emergent SEP-363856 SAEs have been reported in less than 5% of exposed subjects, most of which occurred in subjects with schizophrenia enrolled in studies SEP361-201 and SEP361-202, and which were consistent with the manifestations of the underlying disease. A single report of hypotension experienced by a 31 year old male normal healthy volunteer in study SEP361-104 was assessed as serious and resolved 20 minutes after receiving treatment with oral fluids and oxygen. Across the SEP-363856 development program, AEs leading to study drug or study discontinuation have generally occurred in subjects with schizophrenia and have been consistent with the underlying disease. The most common AEs across the studies were somnolence, nausea, dizziness, headache, fatigue, and orthostatic hypotension.

Taken together, these results demonstrated that SEP-363856 has an acceptable safety profile as well as robust CNS engagement and activity that suggest antipsychotic properties.

The present study is being conducted to evaluate initial safety, tolerability, and efficacy of flexible dosing of SEP-363856 in adult subjects with PDP.

4.3. Risk-Benefit Assessment

Overall across clinical studies conducted to date, SEP-363856 has been generally well-tolerated. The majority of AEs have been mild or moderate and infrequently led to treatment discontinuation. SAEs have also been infrequent and have been reported predominantly in studies conducted in subjects with schizophrenia. A single event of hypotension experienced by a normal healthy volunteer was assessed as serious. TEAEs of hypotension and orthostatic hypotension observed to date have occurred in studies of both normal healthy volunteers and in subjects with schizophrenia, have been transient, mild or moderate in intensity and the majority did not require concomitant treatment or intervention. The PK and safety profiles observed in adult subjects from completed Phase 1 and Phase 2 clinical studies supports the evaluation of flexibly-dosed SEP-363856 at 25, 50 or 75 mg/day in adult subjects with PDP.

PD is a chronic neurodegenerative disorder that affects motor control. It is the second most common neurodegenerative disease after Alzheimer's disease and affects approximately 1 million people in the US and 7 million globally. PDP has been associated with poorer quality of life, increased morbidity and mortality, and increased caregiver burden and nursing home placement (Aarsland-2000). Nuplazid™ (pimavanserin), a selective 5-HT2A inverse agonist, is the first treatment approved for PDP by the US FDA. SEP-363856 has a novel mechanism of action not related to direct antagonism of the D_2 or 5-HT_{2A} receptors and may benefit patients with PDP.

4.4. Hypothesis

4.4.1. Primary Hypothesis

Treatment with SEP-363856 in subjects with PDP will result in a significant reduction in the Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD) total score at Week 6 when compared to placebo.

Let μ_{SEP} and μ_{PBO} represent the mean changes from Baseline at Week 6 in SAPS-PD total score for the SEP-363856 and placebo arms, respectively. The following hypothesis will be tested to compare the mean change values between the SEP-363856 group and placebo group at Week 6:

H_0: $\mu_{SEP} = \mu_{PBO}$ versus H_1: $\mu_{SEP} \neq \mu_{PBO}$

5. STUDY OBJECTIVES

5.1. Primary Objective

To evaluate the efficacy of flexibly dosed SEP-363856 (25, 50, or 75 mg/day) in subjects with PDP as measured by the Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD) at Week 6.

5.2. Secondary Objectives

Double-blind Period:

- To evaluate the efficacy of SEP-363856 (25, 50, or 75 mg/day) in subjects with Parkinson's Disease Psychosis as measured by:
  - Neuropsychiatric Inventory (NPI)
  - Clinical Global Impression – Severity (CGI-S)
  - Mini Mental State Examination (MMSE) for cognition

5.3. Safety Objectives

Double-blind period:

- To evaluate the safety and tolerability of SEP-363856 (25, 50, or 75 mg/day) using:
  - Adverse event (AE) reports
  - Clinical laboratory results
  - 12-lead electrocardiograms (ECG)
  - Vital signs
  - Physical and neurological examinations (PE, NE)
  - Body weight, body mass index (BMI)
  - Columbia-Suicide Severity Rating Scale (C-SSRS)

Open Label Period:

- To further evaluate the safety and tolerability of open-label flexibly dosed SEP-363856 (25, 50, or 75 mg/day)
  - Adverse event (AE) reports
  - Clinical laboratory results
  - 12-lead electrocardiograms (ECG)
  - Vital signs
  - Physical and neurological examinations (PE, NE)
  - Body weight and body mass index (BMI)
  - Columbia – Suicide Severity Rating Scale (C-SSRS)

5.4. Other Objectives

Double-blind Period:

- To evaluate the effects of SEP-363856 sleep quality as measured by the Scales for Outcomes in Parkinson's Disease for nighttime sleep quality (SCOPA-NS) and daytime sleepiness (SCOPA-DS).
- To evaluate the effects of SEP-363856 on motor symptoms associated with Parkinson's Disease as measured by the Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and III).

  To evaluate the effects of SEP-363856 on Rapid Eye Movement (REM) Sleep Behavioral Disorder (RBD) symptoms as measured by the RBD questionnaire (RBDQ).

Open Label Period:

- To further evaluate the effectiveness of flexibly-dosed SEP-363856 over 12-weeks of treatment using:
  - Neuropsychiatric Inventory (NPI)
  - Clinical Global Impression-Severity (CGI-S)
  - Mini Mental State Exam (MMSE)
  - SAPS-PD
- To evaluate the effects of SEP-363856 on sleep quality as measured by the Scales for Outcomes in Parkinson's disease for nighttime sleep quality (SCOPA-NS) and daytime sleepiness (SCOPA-DS).
- To evaluate the effects of SEP-363856 on motor symptoms associated with Parkinson's Disease as measured by the Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and III).
- To evaluate the effects of SEP-363856 on Rapid Eye Movement (REM) Sleep Behavioral Disorder (RBD) symptoms as measured by RBD questionnaire (RBDQ).

6. STUDY ENDPOINTS

6.1. Primary Endpoint

The primary endpoint is the change from double-blind (DB) Baseline in total SAPS-PD score at Week 6.

6.2. Secondary Endpoints

Double Blind Period:

- Change from DB Baseline in the CGI-S at Week 6.
- Change from DB Baseline in NPI at Week 6.
- Change from DB Baseline in MMSE at Week 6.

6.3. Safety Endpoints

Double Blind Period:

- The incidence of AEs, SAEs, and AEs (or SAEs) leading to discontinuation during the double-blind period.
- Absolute values and changes from DB Baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], and 12-lead ECGs).
- Frequency of subjects with suicidal ideation or suicidal behavior using the C-SSRS during the double-blind period.

Open-label period:

- The incidence of AEs, serious adverse events (SAEs), and AEs (or SAEs) leading to discontinuation during the open-label (OL) extension and overall.
- Absolute values and changes from DB and OL Baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis), and clinical evaluations (vital signs, body weight, BMI, blood pressure [supine and standing], heart rate [supine and standing], and 12-lead ECGs).
- Frequency of subjects with suicidal ideation or suicidal behavior using the C-SSRS during the open-label extension and overall.

6.4. Other Endpoints

Double Blind Period:

- Change from DB Baseline in nighttime sleep quality as measured by the SCOPA-NS at Week 6.
- Change from DB Baseline in daytime sleepiness as measured by the SCOPA-DS at Week 6.

- Change from DB Baseline in the UPDRS II and III at Week 6.
- Change from DB baseline in RBD symptoms at Week 6 as measured by the RBDQ.

Open Label Period:

- Change from DB and OL Baseline in nighttime sleep quality as measured by the SCOPA-NS at Week 18.
- Change from DB and OL Baseline in daytime sleepiness as measured by the SCOPA-DS at Week 18.
- Change from DB and OL Baseline in the UPDRS II and III at Week 18.
- Change from DB and OL baseline in RBD symptoms at as measured by the RBDQ at Week 18.
- Change from DB and OL Baseline in the CGI-S at Week 18.
- Change from DB and OL Baseline in NPI at Week 18.
- Change from DB and OL Baseline in MMSE at Week 18.
- Change from DB and OL baseline in total SAPS-PD at Week 18.

7. INVESTIGATIONAL PLAN

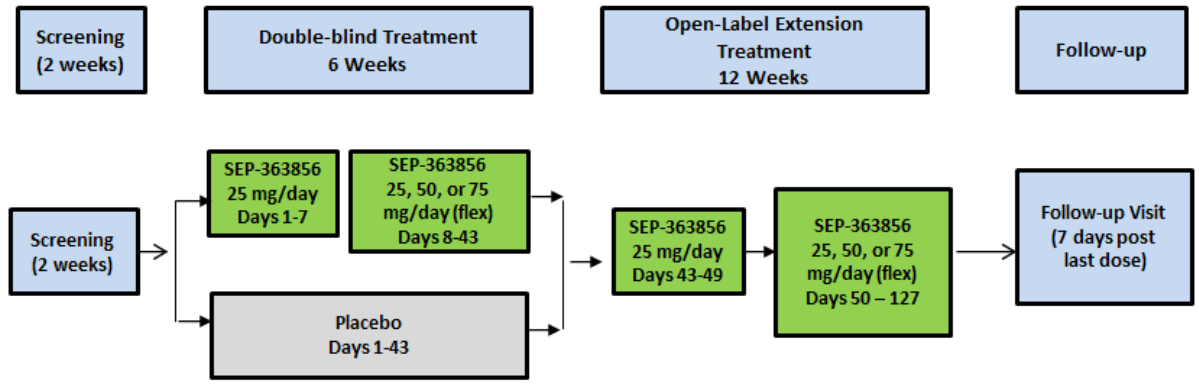
7.1. Overall Study Design

This is a multicenter, randomized, parallel-group, placebo-controlled study evaluating the efficacy, safety, and tolerability of double-blind SEP-363856 flexibly dosed at 25, 50, or 75 mg/day for 6 weeks followed by 12 weeks of open-label extension SEP-363856 flexibly-dosed at 25, 50, or 75 mg/day in male and female subjects ≥ 55 years of age with a clinical diagnosis of PDP. The study will randomize approximately 36 subjects to 2 treatment groups in a 2:1 ratio (approximately 24 subjects to SEP-363856 and 12 to placebo).

The study will consist of 4 periods: Screening/Washout Period (up to 14 days prior to Double-blind Treatment), Double-blind Treatment Period (6 weeks), Open-label SEP-363856 Treatment Period (12 weeks), and Follow-up Period (1 week after last dose). All post-Baseline clinic visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3).

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2 and Table 3, Schedule of Assessments, and Section 11, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic



Note: Double-blind ends with Day 43 assessments; Open-label extension begins Day 43 with first dose in the evening.

Screening/Washout Period (Days -14 to -1):

Subjects who provided written informed consent to participate in the study will be evaluated for eligibility during a screening/washout period of up to 14 days, during which they will be tapered off all antipsychotic or centrally acting anticholinergic medications in a manner that is consistent with labeling recommendations and conventional medical practices. The subject's caregiver must also provide consent for the subject to participate in this study as well as consent for collection of caregiver data as related to the assessment of the subject's neuropsychiatric status as measured by the NPI. The screening visit may occur over more than one day. The washout period can start immediately at screening. Prior treatment with antipsychotic agents must be discontinued at least 5 half-lives prior to the site performing the NPI and MMSE screening assessments.

Subjects who meet the study entry criteria at screening (see inclusion criteria in Section 8.1) and have gone through the washout period, as necessary, will enter the 6-week double-blind treatment period.

Double-blind Treatment Period (6 weeks):

Randomization/Treatment:

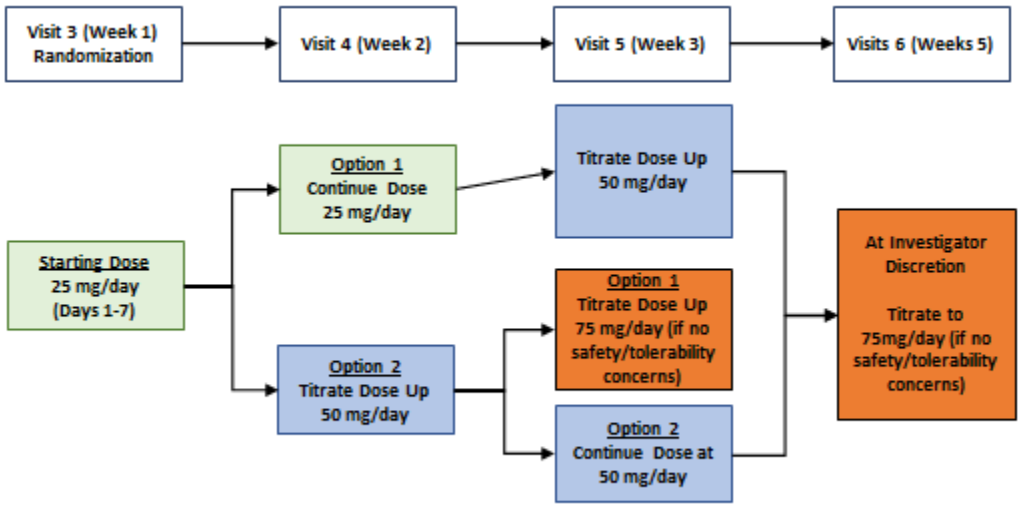
At Baseline (Day 1, Visit 3), subjects who have successfully completed screening/washout (see randomization criteria in Section 8.3) will be randomly assigned via interactive voice/web response system (IXRS) in a 2:1 ratio to SEP-363856 or placebo. Study drug dosing will begin following completion of the baseline assessments on the same day (Day 1, Visit 3). Double-blind study drug will be taken in-clinic at the Baseline visit (Day 1) and on visit days when subject titrates up. Subsequent doses starting the following day should be taken at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bed-time. After receiving the initial dose (Day 1) and after each up-titration, subjects will remain in the clinic for 2 hours of clinical observation, which will include assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose), additional medical assessments can be performed as needed per investigator discretion. Findings will be collected on appropriate case report forms (CRFs). Subjects will be discharged home if medically stable. Dosing will continue QD at bedtime for the remainder of the study, without regard for food.

Subjects will have clinic visits and procedures as outlined in Table 2. Telephone calls to the subjects will be made on the first 2 days after a dose adjustment. An unscheduled visit will be made as early as possible for dose adjustments or evaluation of safety/tolerability issues. Efforts will be made to ensure that the subject's caregiver remains the same for all study visits. All post-Baseline clinic visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3).

Subjects randomized to SEP-363856 will receive flexible doses of SEP-363856 (25, 50, or 75 mg/day). Subjects will receive SEP-363856 25 mg/day for 1 week (Days 1 - 7). If there are no safety or tolerability issues, subjects should be up-titrated to 50 mg/day at Visit 4 (Week 2). Subjects still receiving SEP-363856 25 mg/day must have their dose up-titrated to 50 mg/day at Visit 5 (Week 3), unless approved to stay at 25 mg/day by the Medical Monitor due to safety and tolerability concerns. At the investigator's discretion, subject may up-titrate to 75 mg during scheduled visits. During the double-blind period up-titration will not be allowed after Visit 6 (Week 5). Dose reductions to 50 mg/day or 25 mg/day will be allowed by 1 dose level, at any

time for reasons of safety and tolerability. During the double-blind period, following a dose reduction, subjects may increase their dose to the next dose level up to Visit 6 (Week 5) at the Investigator's discretion and only during scheduled visits. If safety or tolerability issues result in study medication dose discontinuation or reduction, the Investigator must contact the Medical Monitor before the subject is rechallenged. The study medication can be re-introduced if agreed to by the Investigator and Medical Monitor.

Figure 2: Dosing Schematic



Notes:

- Dose reduction is allowed at any time for reasons of safety or tolerability; during unscheduled or scheduled visits.
- During the Double-Blind Period, up-titration to a prior dose level is allowed at Investigator's discretion and only during a scheduled visit.
- At Visit 5 (Week 3), the dose should be up titrated to 50mg/day. In the event of tolerability/safety concerns, the dose may remain at 25 mg/day with Medical Monitor approval.
- Visit 6 (Week 5) is the last visit where up-titration can occur during the Double-Blind Period.

Open-label Extension Period:

For subjects who complete the DB period and continue into the Open-label (OL) period, the baseline visit for the open-label period will be the end of double-blind treatment period (Week 6 of DB period). Drug will be taken in-clinic on OL Day 1 (Study Day 43) of the open-label period and on study visit days when subject up- titrates; with subsequent dosing starting the following day at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bedtime. After receiving the initial dose of 25 mg (OL Day 1) and after each up-titration, subjects will remain in the clinic for 2 hours of clinical observation; which will include assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion. Findings will be collected on appropriate case report forms (CRFs).

Subjects will be discharged home if medically stable. Dosing will continue once daily (QD) at bedtime for the remainder of the study, without regard for food.

The total daily dose will remain between 25 mg/day and 75 mg/day for the 12-week treatment period. Subjects will receive SEP-363856 25 mg/day for 1 week. If there are no safety or tolerability issues, subjects should be up-titrated to 50 mg/day at Visit 8 (OL Week 2; OL Day 8). Subjects still receiving SEP-363856 25 mg/day must have their dose up- titrated to 50 mg/day at Visit 9 (OL Week 3), however may remain at 25 mg/day due to safety/tolerability issues with medical monitor approval. At the investigator's discretion, subject may up-titrate to 75 mg during scheduled visits.

Dose reductions will be allowed by 1 dose level, at any time for reasons of safety and tolerability. Following a dose reduction, subjects may increase their dose at the Investigator's discretion and only during scheduled visits. If safety or tolerability issues result in study medication dose discontinuation or reduction, the Investigator must contact the medical monitor before the subject is re-challenged. The study medication can be re-introduced if agreed on by the Investigator and Medical Monitor.

A minimum of 7 days is required between dose increases. Dose decreases may be made at any time, at the Investigator's discretion, for reasons of safety or tolerability. If, in the judgment of the investigator, the subject does not tolerate the minimum required dose (25 mg/day), the subject will be discontinued from the study.

During the OL extension treatment period, subjects will return to the clinic and have assessments as described in Table 3.

Telephone calls to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease). At Study Week 12 and Study Week 16 (midpoint between Visit 11 and Visit 12, and midpoint between Visit 12 and Visit 13) the site staff will contact the subject via telephone in order to monitor for AEs, SAEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration, and upcoming visits. If necessary, an unscheduled visit will be made as early as possible for dose adjustments or evaluation of safety/tolerability issues.

Follow-up Period (7 days):

All subjects who either complete the treatment period or discontinue early will have a follow-up visit for final safety assessments 7 days (± 2 days) after the last dose of study drug.

7.1.1. Study Assessments

Double Blind Period:

Efficacy will be assessed by the SAPS-PD, the NPI, CGI-S, and the MMSE. Safety and tolerability will be monitored throughout the study by collection of AEs, clinical laboratory parameters, ECGs, vital signs, PE and NE, C-SSRS, body weight, and BMI. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation.

The quality of nighttime sleep as well as daytime sleepiness will be assessed by the SCOPA-NS and the SCOPA-DS, respectively. The effects of SEP-363856 on motor symptoms will be

assessed by the UPDRS II and III, and its effects on REM behavioral disorder assessed by the RBDQ.

Blood samples for the determination of SEP-363856 and SEP-363854 plasma concentrations will be collected as described in Table 2. Population pharmacokinetic (POPPK) analyses will be performed utilizing the data, results of which will be provided in a separate report.

OL Extension Period:

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

Efficacy will be assessed by the NPI, the CGI-S, and the MMSE.

The quality of nighttime sleep as well as daytime sleepiness will be assessed by the SCOPA-NS and the SCOPA-DS, respectively. The effects of SEP-363856 on motor symptoms will be assessed by the UPDRS II and III, and its effects on REM behavioral disorder assessed by the RBDQ.

Blood samples for the determination of SEP-363856 and SEP-363854 plasma concentrations will be collected as described in Table 3. Population pharmacokinetic (POPPK) analyses will be performed utilizing the data, results of which will be provided in a separate report.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

The randomization schedule will be generated by a non-study biostatistician. Once a subject is deemed eligible to be randomized at Day 1 (Visit 3), the IXRS will perform treatment assignment. Subjects will be randomized to one of the following treatment groups for the double-blind treatment period in a 2:1 ratio (SEP-363856:placebo):

- SEP-363856 (25, 50 or 75 mg/day flexible dosing QD for 6 weeks)
- Placebo (QD for 6 weeks)

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

7.2.2. Blinding

During the Double-blind Treatment Period, subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods; (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of bioanalytical personnel involved in the analysis of PK samples; (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

Actual subject identity for plasma concentrations of SEP-363856 and SEP-363854 will not be disclosed before the database lock and the unblinding of the double-blind treatment.

After completion of the DB treatment period, all subjects will receive unblinded flexibly dosed SEP-363856.

7.2.3. Emergency Unblinding Procedures

In the case of a medical emergency, where knowledge of study drug by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IXRS. The date and reason for unblinding are to be documented in the source documents. Any subject for whom the treatment assignment was unblinded is to be discontinued from further study participation. The subject should return for a final study assessment as described in Section 11.9.9.

7.3. Rationale

7.3.1. Rationale for the Study Design

This is a multicenter, randomized, parallel-group, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of SEP-363856 flexibly dosed at 25, 50, or 75 mg/day for 6 weeks followed by 12 weeks of open-label extension of SEP-363856 flexibly-dosed at 25, 50, or 75 mg/day in male and female subjects ≥ 55 years of age with a clinical diagnosis of PDP. The collection of safety and efficacy data in an elderly population will further support the development program for SEP-363856, which to date has collected data in adult healthy volunteer subjects and younger adult patients with acute schizophrenia, age 18-40 years. There are no data in a patient population > 65 years treated with SEP-363856. The open-label extension will provide additional safety, tolerability and efficacy data of SEP-363856 flexibly dosed at 25, 50, or 75 mg/day for an additional 12 weeks in subjects with a clinical diagnosis of PDP.

7.3.2. Rationale for the Dosages

In the present study, flexible doses of SEP-363856 at 25, 50, or 75 mg/day will be investigated.

Selection of this dose range was guided by the following:

- Maximum tolerated dose (MTD) determined for single doses of SEP-363856 administered to healthy adult male subjects in Study SEP361-101 (50 mg)
- Doses administered to healthy adult male subjects (Studies SEP361-103 and SEP361-104) in which SEP-363856 was found to have robust CNS activity (50 mg)
- Study SEP361-104 functional magnetic resonance imaging (fMRI) study in healthy male and female subjects with high or low schizotype characteristics demonstrating effects of SEP-363856 (50 mg) in brain regions such as the orbito-frontal cortex, insula and striatum
- Study SEP361-108 in patients with narcolepsy-cataplexy, suppression of REM sleep at 25 and 50 mg QD demonstrating CNS activity

- In the open-label study SEP361-106 (Part 2) that investigated the PK and efficacy of SEP-363856 at 75 mg/day for 28 days in male and female subjects with schizophrenia, improvement in efficacy measures (PANSS total score, CGI-S) compared with Baseline

Dose selection is further supported by acceptable safety and tolerability data from the 7-day (10 - 75 mg, QD) and open-label 28-day (75 mg, QD) in patients with schizophrenia. Phase 1 studies have also demonstrated dose-proportional increases in plasma SEP-363856 exposure (C_{max} and AUC).

SEP-363856 has not been administered in patients with PD or PDP prior to this study. The study will therefore start at the lowest dose that showed CNS activity (25 mg).

7.4. Prevention of Missing Data

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

- Allowance of a dose reduction. Dose reductions to 50 mg/day or 25 mg/day will be allowed by 1 dose level, at any time for reasons of safety and tolerability.
- Allowance of concomitant nonpsychotropic medications during study participation.
- Use of study centers with a good track record of enrolling and following eligible subjects.
- Train the study centers on the importance of continued follow-up and on the informed consent process, ensuring subjects and caregivers understand the commitment they are making, including the intent to complete the trial.
- Monitor data collection at the site level for adherence during the study.

Please see Section 15.3.11 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Subject, caregiver, and/or legally authorized representative understands and is willing to sign informed consent authorizing subject to participate in the study.
2. Subject must be willing and able to comply with the study procedures and visit schedules and must be able to follow verbal and written instructions.
3. Subject is male or postmenopausal female ≥ 55 years of age.
4. Subject meets established diagnostic criteria for Parkinson's disease of at least one year duration, consistent with the UK Brain Bank criteria.
5. Subject has psychotic symptoms that began after the diagnosis of PD for at least one month, occurring at least weekly in the month prior to screening (according to subject or caregiver), and severe enough to warrant treatment with antipsychotics.
6. Subject has a combined score of at least 6 or an individual score of at least 4 on the Neuropsychiatric Inventory (NPI) Item A (delusions) and/or Item B (hallucinations). This criterion must be met at Visit 1 and Visit 3.
7. Subject has a Mini Mental State Examination (MMSE) score > 16 points out of 30.
8. Subject has a caregiver (eg, spouse or family member) who will be required to attend all visits and is able to provide study information on various scales such as the NPI.
9. Subject is taking antiparkinsonian drugs or deep brain stimulation, with a stable dose/dose regimen and settings for 1 month before screening.
10. Female subject must be postmenopausal defined as being amenorrheic for greater than two years with an appropriate clinical profile.
11. Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use acceptable methods of birth control from screening until at least 30 days after the last study drug administration.
12. Subject is, in the opinion of the Investigator, medically stable 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).
13. Subject has had a stable living arrangement at the time of screening.

8.2. Subject Exclusion Criteria

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

1. Subject has psychosis secondary to other toxic or metabolic disorders.

2. Subject has atypical Parkinson's disease, Parkinsonism secondary to medication or other neurodegenerative disorders, such as progressive supranuclear palsy or multiple system atrophy.
3. Subject has dementia diagnosed concurrent with or before Parkinson's disease, motor symptoms that began less than one year before the onset of dementia or symptoms consistent with the diagnosis of Lewy Body Dementia (DLB), or if the psychosis occurred after ablative stereotaxic surgery.
4. Subject failed 2 or more antipsychotic agents given at adequate doses for at least 4 weeks within 1 year before screening. Treatment failure is defined as a complete lack of efficacy. Subjects who had a partial response or who discontinued treatment for reasons of tolerability will be allowed.
5. Subject has had a stroke or other uncontrolled serious medical or neurological illness within 6 months of baseline.
6. Subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS at Screening (the past one month) or baseline (ie, since last visit).
7. Subject does not tolerate venipuncture or has poor venous access that would cause difficulty for collecting blood samples.
8. Subject has participated in an investigational drug study and received investigational drug within 30 days (or longer if the half-life is known to be ≥ 150 hours) prior to the screening visit, or who is currently participating in another interventional study. Observational studies are not exclusionary. Subject has previously received SEP-363856.
9. 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.
10. Subject has hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular, hepatic, neurologic, or allergic disease that is clinically significant or unstable as judged by the Investigator.
11. 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. Pituitary tumors of any duration are excluded.
12. Subject has, in the opinion of the Investigator, a disorder or history of a condition such as a clinically significant abnormality of the hepatic or renal system or a history of malabsorption, or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, bowel resection, or any surgical procedure) that may interfere with drug absorption, distribution, metabolism, excretion.
13. Subject has known or suspected Alcohol or Substance Use Disorder as defined by DSM-5. The only exceptions are caffeine or nicotine.

14. Subject has a clinically significant abnormal 12-lead ECG that may result in the subject's inability to complete the study, as judged by the Investigator.
15. Subjects with known human immunodeficiency virus (HIV) seropositivity will be excluded.
16. Female subject who is pregnant or lactating.
17. Subject has an active and unstable psychiatric disorder as judged by the Investigator.
18. Subject is at significant risk of harming him/herself or others according to the Investigator's judgment.
19. Subject has attempted suicide within 3 months prior to screening.
20. Subject has a history of allergic reaction or suspected sensitivity to any substance that is contained in the study drug formulation.
21. Subject has any clinically significant abnormal laboratory values (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, serum prolactin, and urine drug screen [Note: Abnormal findings that may be clinically significant or of questionable significance will be discussed with the Medical Monitor prior to including subject.]).
22. Subjects with serum alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 3 times, serum blood urea nitrogen (BUN) or creatinine ≥ 1.5 X the upper limit of the reference ranges provided by the central laboratory require retesting. If on retesting, the laboratory value remains equal to or above the ULN, the subject will be excluded.
23. Subjects with a random (non-fasting) blood glucose at screening ≥ 200 mg/dL (11.1 mmol/L) and HbA_{1c} ≥ 7% will be excluded.
24. Subject has a prolactin concentration > 100 ng/mL at screening or has a history of pituitary adenoma.
25. Subject has an abnormal BMI that may result in the subject's inability to complete the study, as judged by the Investigator.
26. Subject has experienced significant blood loss (≥ 473 mL) or 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.
27. Subject consumes more than 300 mg of caffeine per day (5 cups of coffee or equivalent in caffeinated beverages).
28. Subject has used disallowed prescription medications (as described in Section 10.3) within 30 days of screening or anticipates the need for any disallowed medication during their participation in this study.
29. Subject is a staff member or the relative of a staff member.
30. Subject is in the opinion of the Investigator, unsuitable in any other way to participate in this study.

8.3. Randomization Criteria

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

1. Subject must have a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI) Item A (delusions) and/or Item B (hallucinations) at Baseline (Day 1).
2. Subject must continue to meet all other inclusion criteria and none of the exclusion criteria at Baseline (Day 1).

8.4. Continuation into Open-label Extension Criteria

To qualify for continuation into the open-label extension period, subjects must meet the following criteria:

- Subject must have completed the 6-week double-blind treatment.
- Subject has not taken any medication other than the study drug for the purpose of controlling PDD symptoms.
- There has been no clinically significant change in the subject's medical condition or Parkinson's disease, in the opinion of the investigator.
- Subject has not answered "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at any time during the DB treatment period.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

Table 6: Investigational Product

Attribute	Investigational Product			
Product name	SEP-363856	SEP-363856	SEP-363856	Placebo
Dosage form	Capsule	Capsule	Capsule	Capsule
Unit dose	25 mg	50 mg	75 mg	NA
Route of administration	Oral	Oral	Oral	Oral
Physical description	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule
Excipients	None	None	None	Microcrystalline cellulose

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

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

9.2.2. Labeling Description

All packaging for the study drugs will be labeled with:

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

9.3. Study Drug Storage

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

9.4. Dispensing of Study Drug

An interactive voice/web response system (IXRS) will be used to manage subject screening and randomization. The IXRS is an integrated web-based subject and drug management system.

Study drug blister cards will be assigned by the IXRS based on the treatment schedule and dose adjustment criteria. The IXRS will generate instructions for which study medication unit/number to assign to a subject. Each subject will be dispensed one to four 9-day blister cards per scheduled visit depending on the timing of the next scheduled visit (see Table 2 and Table 3).

Study drug will be taken in-clinic at the Double-blind Baseline visit (Day 1), at Open-label baseline Visit 7 (Day 43; OL Day 1), and on visit days when subject titrates up; with subsequent dosing starting the following day at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bedtime. Study drug may be taken without regard for food.

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

9.5. Study Drug Accountability

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

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

The Investigator or designee will maintain accountability records, including availability of study drug received, and study drug dispensation and return. The Investigator or designee will collect and document the status of all used and unused study drug from study subjects at appropriate study visits per Sponsor’s instructions.

9.6. Study Drug Handling and Disposal

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

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

10. TREATMENT OF SUBJECTS

10.1. Study Drug

Active and matched placebo doses (study drug) will be administered QD daily during the double-blind treatment period. Double-blind study drug (active or matched-placebo, as applicable) dosing will be taken in-clinic at Visit 3 (Day 1) and Visit 7 (Day 43; OL Baseline Day 1); as well as on visit days when a subject up-titrates. Subsequent doses starting the following day should be taken at bedtime. For the remainder of the study, subjects will take one capsule of study drug per day at approximately the same time each evening at bedtime.

All study drug doses will consist of capsule(s) containing either SEP-363856 or matched placebo (in order to maintain blinding) administered orally QD.

Subjects may take study drug without regard for food.

Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected predose (before study drug administration) and postdose as describe in Table 2 and Table 3 as well as in Section 22. The time and date of the 3 previous doses of study drug, time, and date of sampling must be recorded. The time and date of food intake will be recorded on Day 43 when blood samples are collected for determination of plasma SEP-363856 concentrations.

10.1.1. Dosage Adjustment Criteria

During the DB treatment period:

Subjects randomized to SEP-363856 will receive flexible doses of SEP-363856 (25, 50, or 75 mg/day). Subjects will receive SEP-363856 25 mg/day for 1 week (Days 1 - 7). If there are no safety or tolerability issues, subjects should be up-titrated to 50 mg/day. Subjects still receiving SEP-363856 25 mg/day must have their dose up- titrated to 50 mg/day at Visit 5 (Week 3). At the investigator's discretion, subject may up-titrate to 75 mg during scheduled visits. Up-titration will not be allowed after Visit 6 (Week 5). Dose reductions will be allowed by 1 dose level, at any time for reasons of safety and tolerability. Following a dose reduction, subjects may increase their dose to the next dose level up to Visit 6 (Week 5) at the Investigator's discretion and only during scheduled visits. If safety or tolerability issues result in study medication dose discontinuation or reduction, the Investigator must contact the medical monitor before the subject is re-challenged. The study medication can be re-introduced if agreed on by the Investigator and Medical Monitor.

Subjects randomized to placebo will receive placebo treatment throughout the study.

During the OL extension treatment period:

Subjects will receive flexible doses of SEP-363856 (25, 50, or 75 mg/day). Subjects will receive SEP-363856 25 mg/day for 1 week. If there are no safety or tolerability issues, subjects should be up-titrated to 50 mg/day at Visit 8 (OL Week 2; OL Day 8). Subjects still receiving SEP-363856 25 mg/day must have their dose up- titrated to 50 mg/day at Visit 9 (OL Week 3). At the investigator's discretion, subject may up-titrate to 75 mg during scheduled visits. Dose reductions will be allowed by 1 dose level, at any time for reasons of safety and tolerability. Following a dose reduction, subjects may increase their dose at the Investigator's discretion and

only during scheduled visits. If safety or tolerability issues result in study medication dose discontinuation or reduction, the Investigator must contact the medical monitor before the subject is re-challenged. The study medication can be re-introduced if agreed on by the Investigator and Medical Monitor.

10.2. Treatment Compliance

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

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

10.3. Concomitant Medications

The following information on all medication administered between screening and study follow-up or at discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, indication, and whether the medication was started after last dose of study medication.

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).

Collection of prior and concomitant medication review is described in Section 11.2.

10.3.1. Prior Medications

Subjects taking nonpsychotropic medications must be on a stable dose within 30 days prior to screening and maintain the dose and regimen throughout the study.

Subjects must maintain their anti-Parkinson's medications on a stable dose throughout the study. Dose adjustments will not be allowed, unless approved by the medical monitor.

Prior treatment with antipsychotic agents (including pimavanserin) must be discontinued within 5 half-lives prior to randomization. Prior treatment with centrally acting anticholinergic agents including but not limited to diphenhydramine, trihexyphenidyl, and biperidin must be discontinued no less than two weeks prior to randomization. Antipsychotic and centrally acting anticholinergic medications are prohibited during the course of the study.

Use of antidepressant, anxiolytic, and sleep medications is allowed. The dose of these medications must be a stable dose within 30 days prior to screening and be maintained throughout the study.

Use of acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine is allowed but the dose of these medications must be stable for at least 30 days prior to screening and must be maintained throughout the study.

The addition of antipsychotic agents, central acting anti-cholinergic agents, including but not limited to diphenhydramine, trihexyphenidyl, and biperiden, antidepressants, hypnotics or any other aids used for sleep is prohibited.

Medications for the treatment of anxiety/agitation such as lorezapam up to a dose of 6 mg/day or its equivalent are permitted with prior authorization from the medical monitor and should not be used within 8 hours prior to efficacy assessments.

10.3.2. Rescue Medication

Antipsychotic medication will not be allowed during the course of study. Antianxiety medication to treat agitation and anxiety is permitted with prior authorization from the Medical Monitor.

10.3.3. Restricted Therapies

Subjects will be allowed to continue with ongoing physical or occupational therapy initiated prior to screening which aims to address their physical disabilities. No new therapies should be initiated during the course of the study.

10.4. Other Restrictions

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

10.5. Description of Study Periods

10.5.1. Description of Study Periods

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

Table 7: Description of Study Periods

Study Period	Visit Number	Study Day[a] (OL Study Day)	Inpatient/Outpatient
Screening	Visit 1	-14 to -1 (NA)	Outpatient
Double-blind Baseline	Visit 3	1 (NA)	Outpatient
Double-blind	Visit 4	8 (± 2 days) (NA)	Outpatient
Double-blind	Visit 5	15 (± 2 days) (NA)	Outpatient
Double-blind	Visit 6	29 (± 2 days) (NA)	Outpatient
Double-blind End/ Open-label baseline	Visit 7	43 (± 2 days) (OL Day 1)	Outpatient
Open-label Extension	Visit 8	50 (± 2 days) (OL Day 8)	Outpatient
Open-label Extension	Visit 9	57 (± 2 days) (OL Day 15)	Outpatient
Open-label Extension	Visit 10	64 (± 2 days) (OL Day 22)	Outpatient
Open-label Extension	Visit 11	71 (± 3 days) (OL Day 29)	Outpatient
Open-label Extension	Visit 12	99 (± 3 days) (OL Day 57)	Outpatient
Open-label Extension	Visit 13 / EOT / ET	127 (± 3 days) (OL Day 85)	Outpatient
Follow-up	Visit 14	7 days after last dose (± 2 days)	Outpatient

[a] Study Day is based on Visit 3 (Day 1) and OL Day is based on Visit 7 (Study Day 43).

10.6. Guidance for Overdose

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

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. Summary of assessments to be conducted at each visit for the DB treatment period and OL extension are presented in Table 2 and Table 3, respectively.

Efforts will be made to ensure that the subject's caregiver remains the same caregiver for all study visits. For this study a caregiver should be involved in the daily care of the subject and have detailed knowledge of the subject's behavior.

The same study site rater should perform the same scale assessment(s) for a given subject, whenever possible.

All post-Baseline DB treatment visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3).

The SAPS-PD, CGI-S, MMSE, UPDRS II, UPDRS III, and neurological exam should be performed during the subject's on-periods (ie, at a time when the subject shows no clinical evidence of worsening in their Parkinson's symptoms, as determined by the site investigator). The NPI is administered to the caregiver only and should be completed referencing the subject's on-period.

For this study 1 week is defined as 7 days and 1 month is defined as 4 weeks (28 days).

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. The Medical History will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

At screening subjects will be checked for multiple study enrollment by clinical site staff using available registries of subjects participating in clinical trials.

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 taken within 30 days prior to screening visit in the eCRF. The following parameters will be recorded for all prior and 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).

Site staff will also record all historical and current concomitant anti-psychotic medication(s) or centrally acting anticholinergic agents that the subject has taken on the corresponding eCRF page.

11.3. Efficacy Assessments

11.3.1. Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD)

The Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD) is a Parkinson's disease-adapted subset of nine items derived from the Scale for Assessment of Positive Symptoms (SAPS), including seven items assessing individual symptoms, a global hallucinations item and a global delusions item (Cummings-2014). The items were selected based on their frequency and face validity. Principal component analysis was consistent with a 4-factor structure with delusions and visual, auditory and somatic delusions as distinct constructs (Voss-2013). The SAPS-PD will be performed for this study.

The SAPS was originally developed for the assessment of psychotic symptoms in schizophrenia. The SAPS assesses four symptom clusters (hallucinations, delusions, bizarre behavior, and positive formal thought disorder). The items assessed in each of these clusters are rated based on frequency, and the global score item in each cluster is based on both the frequency and extent to which symptoms disrupt functioning.

For this study, the SAPS-PD will be administered by an approved, trained, and calibrated group of blinded Independent Central Raters. The Independent Central Raters will administer the SAPS-PD at study visits 3-7 via live recorded videoconference. Independent Central Raters must have clinical experience with Parkinson's disease patients and caregivers, hold an advanced medical or mental health degree and must successfully complete all applicable study-related training. In order to rate in the study, the Independent Central Rater must be vetted and approved by both Bracket and Sunovion, and must maintain valid Rater Certification on the SAPS-PD. Inter-rater reliability exercises will be conducted at regular intervals with recalibration training provided as needed.

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

The Clinical Global Impression – Severity Scale (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 - 2 minutes (Guy-1976; Williams-2000). The CGI-S rating instrument will be performed by the rater using a paper version of the assessment.

11.3.3. Neuropsychiatric Inventory (NPI)

The Neuropsychiatric Inventory (NPI) (Cummings-1994) is a 12-item behavior rating scale composed of a structured interview of the caregiver, which assess psychiatric disturbance. In this study, the entire NPI will be administered and will be considered a secondary outcome measure. Scores on Item A (delusions) and Item B (hallucinations) will be considered as part of the inclusion criteria. Both the frequency and the severity of each behavior are determined.

The NPI is a rater administered, structured interview administrated to caregivers of dementia patients. A gating question is asked about each sub-domain. If the responses to these questions indicate that the patient has problems with a particular sub-domain of behavior, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms on a 4-point scale and their severity on a 3-point scale (Cummings-1997).

The NPI rating instrument will be performed by the rater using a paper version of the assessment. The same caregiver should be the informant for the NPI whenever possible.

11.3.4. Mini Mental State Examination (MMSE) for Cognition

The Mini Mental State Examination (MMSE) for Cognition (Folstein-1975) is a brief instrument, used to assess cognitive function, consisting of 11 tests including orientation, memory (recent and immediate), concentration, language, and praxis. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. It is based on the performance of the subject and takes approximately 5 to 10 minutes to administer.

The MMSE rating instrument will be performed by the rater using a paper version of the assessment.

11.4. Safety Assessments

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

11.4.1. Adverse Events

Pretreatment events will be collected for each subject at Visits 1 and 2 (ie, prior to first dose administration).

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.

11.4.2. Clinical Laboratory Tests

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

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

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

11.4.3. Vital Signs

Blood pressure, respiratory rate, oral temperature, and pulse rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and pulse rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse

rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

11.4.4. Electrocardiograms (ECGs)

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. Refer to Section 20, Appendix I for additional information. ECG parameters to be collected include ventricular heart rate (beats/min), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec), and overall ECG interpretation (Normal, Abnormal not clinically significant [NCS], Abnormal clinically significant [CS]).

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

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

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

11.4.5. Physical and Neurological Examination

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

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

11.4.6. Height, Weight, and BMI

Weight will be measured in kilograms. Weight will be collected per the Schedule of Assessments (see Table 2 and Table 3). 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.

11.4.7. Safety Scales

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

The Columbia-Suicide Severity Rating Scale (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. For all visits from Visit 2 onward, the "Since Last Visit" version of the C-SSRS will be used.

11.5. Population Pharmacokinetic Assessments

All blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be obtained at the same time that other blood samples are taken whenever possible. Placebo samples will not be analyzed. The time and date of the 3 previous doses of study drug, date, and clock time of sampling must be recorded. Date and clock time of food intake must be recorded on Day 43 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. POPPK analysis will be performed using plasma SEP-363856 concentrations; the results of which will be reported separately. The relationship between SAPS-PD total score and plasma SEP-363856 exposure will be explored using population PK/pharmacodynamics 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 to plasma for SEP-363856 and SEP-363854 concentrations.

11.6. Pharmacokinetic/Pharmacodynamic Assessment

The relationship between SAPS-PD total score and plasma SEP-363856 exposure will be explored using population PK/pharmacodynamics methods, and reported separately.

11.7. Pharmacogenomic Assessments

If a subject and/or legally authorized representative have consented to have a deoxyribonucleic 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 at Visit 3 (Baseline). Samples should not be collected if the subject and/or legally authorized representative have 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). The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on SEP-363856 plasma exposure will be explored and reported separately. See Section 23, Appendix IV for details including instructions of PGx sample handling.

11.8. Other Assessments

11.8.1. Scales for Outcomes in Parkinson's Disease for Nighttime Sleep Quality (SCOPA-NS) and Daytime Sleepiness (SCOPA-DS)

The Scales for Outcomes in Parkinson's Disease Sleep Scale (SCOPA) is a self-administered, validated short questionnaire that is used to assess nighttime sleep (NS) problems and daytime sleepiness (DS) in subjects with Parkinson's disease. It takes about 10 min to complete. The NS subscale addresses NS problems in the past month and includes 5 items with 4 response options ranging from 0 (not at all) to 3 (a lot). The maximum score of this subscale is 15, with higher scores reflecting more severe sleep problems. One additional question evaluates overall sleep quality on a 7-point scale (ranging from slept very well to slept very badly). The score on this item is not included in the score of the NS scale but is used separately as a global measure of sleep quality. The DS subscale evaluates DS in the past month and includes 6 items with 4 response options, ranging from 0 (never) to 3 (often). The maximum score is 18, with higher scores reflecting more severe sleepiness (Marinus-2003).

The SCOPA-DS and SCOPA-NS rating assessments will be performed by the patient using a paper version of the assessment.

11.8.2. Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and UPDRS III)

The Unified Parkinson's Disease Rating Scale (Fahn-1987) is a scale used to follow the longitudinal course of Parkinson's disease. From the original scale, only parts II (Activities of Daily Living) and III (Motor Examination) will be performed in this study. Part II records historical information from the past seven days as how the patient functioned in various activities of daily living. The UPDRS Part III is an objective motor assessment at the time of evaluation. All items from both parts are scored on a 5-point scale (0 - 4) with higher scores indicating higher severity. The same study site rater should perform both parts' assessments for a given subject whenever possible. The UPDRS rating assessments will be performed by the rater using a paper version of the assessments.

11.8.3. Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire (RBDQ)

The REM Sleep Behavior Disorder Questionnaire (RBDQ) is a 10-item patient self-rated questionnaire addressing the clinical manifestations of REM Sleep Behavior Disorder (RBD). Questions are brief and answered "yes" or "no," with a maximum total score of 13. Items 1 - 4 assess the frequency and content of dreams and their relationship to nocturnal movements and other behavior. Item 5 inquires about self-injuries and injuries to the bed partner. Item 6 assesses specific nocturnal motor behaviors, items 7 and 8 address nocturnal awakenings, item 9 assesses disturbed sleep in general and item 10 queries the presence of any neurological disorder (Stiasny-Kolster-2007, Cummings-2014).

The RBDQ screening questionnaire will be performed by the patient using a paper version of the assessment.

11.9. Study Visits and Assessments

See Table 2 and Table 3 for a summary of procedures at each study visit. See Section 11.9.1 to Section 11.9.12 for detailed information on conducting assessments. All post-Baseline visits will have a window of ± 2 days relative to the date of the Baseline visit (Visit 3).

The SAPS-PD, CGI-S, MMSE UPDRS II, UPDRS III, and neurological exam should be performed during the subject's on-periods (ie, at a time when the subject shows no clinical evidence of worsening in their Parkinson's symptoms, as determined by the site investigator). The NPI is administered to the caregiver only and should be completed referencing the subject's on-period.

When indicated (see Table 2 and Table 3), the SAPS-PD should be collected prior to collecting other scale assessments. The order of performing other scale assesments (NPI, CGI-S, MMSE, UPDRS-II and III, SCOPA-NS, SCOPA-DS, RBDQ, and C-SSRS) is at the discretion of the investigator as long as the NPI is conducted prior to the CGI-S. Not all assessments are required at all visits; see Table 2 and Table 3 for procedures at each visit.

11.9.1. Screening/Washout: Visit 1 (Day -14 to -1)

A unique screening number will be assigned to each subject.

Subjects who fail screening, may be re-screened up to 2 times, if judged appropriate by the Investigator. Re-screened subjects will be re-consented and all Visit 1 procedures will be repeated. A new unique screening number will be assigned to each re-screened subject.

The subject's eligibility assessment will be reviewed by the contract research organization's (CRO) oversight quality team along with the sponsor based on protocol specified inclusion and exclusion criteria. The sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility and will be copied on all communications between the CRO and the site relating to eligibility. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled.

Subjects will be evaluated at the screening visit (1 to 14 days before the baseline visit) to determine their eligibility for the study. This visit may occur over more than one day. The following procedures will be conducted during this visit:

- Obtain signed informed consent and privacy authorization from the subject and caregiver before conducting any other visit procedures.
- Review inclusion and exclusion criteria
- Obtain demographic information
- Prior/concomitant medications
- Medical history
- Psychiatric history/mental status
- Physical and neurological examination

- Height and weight; clinical site staff to calculate and record BMI
- Vital sign measurements (prior to ECG)
- Perform ECG
- Blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel, lipid panel, thyroid panel, and coagulation panel)
- For female subjects, blood samples for serum human chorionic gonadotropin (β-hCG) and serum follicle stimulating hormone (FSH)
- Urine sample for urinalysis and urine drug screen (UDS)
- NPI, must be performed after washout
- MMSE, must be performed after washout
- C-SSRS
- Pretreatment events

11.9.2. Baseline: Visit 3 (Day 1)

The following procedures will be conducted predose during this visit:

- Prior/concomitant medications
- Physical and neurological examination
- Vital sign measurements (prior to ECG)
- Weight
- Perform standard 12-lead ECG.
- Review inclusion and exclusion criteria
- Blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, HbA_{1c}, glucose panel, and lipid panel)
- Perform breath alcohol test
- If subject and caregiver signed separate genetic informed consent, collect blood samples for pharmacogenomics (CYPP450 2D6)
- Urine sample for urinalysis
- Blood sample for determination of plasma SEP-363856 and SEP-363854 (predose, and 1 sample between 1-3 hours post dose)
- SAPS-PD
- NPI
- CGI-S
- MMSE

- UPDRS II and UPDRS III
- SCOPA-DS
- SCOPA-NS
- RBDQ
- C-SSRS
- Adverse events
- Review randomization criteria
- Randomize to treatment
- Dispense study drug
- Administer first study drug dose

After receiving the initial dose, subjects will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion. Findings will be collected on appropriate case report forms (CRFs). Subjects will be discharged home if medically stable. Telephone calls to the subjects will be made on the first 2 days following the visit (see Section 11.9.11).

If subject appears to be symptomatic as assessed by the site during a telephone contact and requires additional assessments in-clinic, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.3. Visit 4 (Day 8 ± 2 days), Visit 5 (Day 15 ± 2 days), and Visit 6 (Day 29 ± 2 days)

The following procedures will be conducted during each visit (unless otherwise specified):

- Prior/concomitant medications
- Study drug accountability
- Dispense study drug
- Vital sign measurements (including orthostatic effects)
- SAPS-PD
- NPI (Visit 5 only)
- CGI-S (Visit 5 only)
- MMSE (Visit 5 only)
- UPDRS II and UPDRS III
- SCOPA-DS (Visit 5 only)
- SCOPA-NS (Visit 5, only)
- RBDQ (Visit 5, only)

- C-SSRS
- Adverse events

If the subject titrates up, the subject will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion.

Telephone calls to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease) (see Section 11.9.11).

If subject appears to be symptomatic as assessed by the site during a telephone contact, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.4. Visit 7 (Study Day 43 [± 2 days], Open-label Baseline, OL Day 1)

The following procedures will be conducted during this visit:

- Prior/concomitant medications
- Study drug accountability
- Dispense Study Drug
- Physical and neurological examination
- Weight
- Vital sign measurements (prior to ECG)
- Perform standard 12-lead ECG
- Blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, HbA_{1c}, glucose panel, and lipid panel)
- Urine sample for urinalysis and urine drug screen
- Blood sample for determination of plasma SEP-363856 and SEP-363854, 12 ± 4 hours after the Day 42 dose
- Perform breath alcohol test
- SAPS-PD
- NPI
- CGI-S
- MMSE
- UPDRS II and UPDRS III
- SCOPA-DS
- SCOPA-NS
- RBDQ

- C-SSRS
- Adverse events
- Review Continuation Criteria for Open-label extension
- Administer first open-label study drug dose

After receiving the initial dose of OL study drug, subjects will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion. Findings will be collected on appropriate case report forms (CRFs). Subjects will be discharged home if medically stable. Telephone calls to the subjects will be made on the first 2 days following the visit (see Section 11.9.11).

11.9.5. Visit 8 (Day 50 ± 2 days; OL Day 8),

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability
- Dispense Study drug
- Vital sign measurements (prior to ECG)
- NPI
- CGI-S
- MMSE
- UPDRS II and UPDRS III
- C-SSRS
- Adverse events

If the subject titrates up, the subject will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion.

A telephone calls to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease) (see Section 11.9.11).

If subject appears to be symptomatic as assessed by the site during a telephone contact, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.6. Visit 9 (Day 57 ± 2 days; OL Day 15) and Visit 10 (Day 64 ± 2 days; OL Day 22)

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability

- Dispense Study drug
- Vital sign measurements
- UPDRS II and UPDRS III
- C-SSRS
- Adverse events

If the subject titrates up, the subject will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion.

A telephone calls to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease) (see Section 11.9.11).

If subject appears to be symptomatic as assessed by the site during a telephone contact, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.7. Visit 11 (Day 71± 3 days; OL Day 29)

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability
- Dispense Study drug
- Physical and neurological examination
- Vital sign measurements (prior to ECG)
- Weight
- Perform standard 12-lead ECG
- Blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, HbA_{1c}, glucose panel, and lipid panel)
- Blood sample for determination of plasma SEP-363856 and SEP-363854, 12 ± 4 hours after the Day 70 (OL Day 28) dose
- Urine sample for urinalysis and urine drug screen
- Perform breath alcohol test
- NPI
- SAPS-PD
- CGI-S
- MMSE
- UPDRS II and UPDRS III

- SCOPA-DS
- SCOPA-NS
- RBDQ
- C-SSRS
- Adverse events

If the subject titrates up, the subject will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion.

A telephone call to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease) (see Section 11.9.11).

If subject appears to be symptomatic as assessed by the site during a telephone contact, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.8. Visit 12 (Day 99 ± 3 days; OL Day 57)

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability
- Dispense Study drug
- Vital sign measurements
- NPI
- SAPS-PD
- CGI-S
- MMSE
- UPDRS II and UPDRS III
- C-SSRS
- Adverse events

If the subject titrates up, the subject will remain in the clinic for at least 2 hours of clinical observation, which will include periodic assessments of orthostatic vital signs (1 hour [± 15 min] and 2 hours [± 15 min] post dose); additional medical assessments can be performed as needed per investigator discretion.

A telephone call to the subjects will be made on the first 2 days after a dose adjustment (increase or decrease) (see Section 11.9.11).

If subject appears to be symptomatic as assessed by the site during a telephone contact, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.9. Visit 13 (Day 127± 3 days; OL Day 85) / End of Treatment (EOT) / Early Termination

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability
- Physical and neurological examination
- Vital sign measurements (prior to ECG)
- Weight
- Perform standard 12-lead ECG
- Blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, HbA_{1c}, glucose panel, and lipid panel)
- Blood sample for determination of plasma SEP-363856 and SEP-363854, 12 ± 4 hours after the Day 126 (OL Day 84) dose
- Urine sample for urinalysis and urine drug screen
- Perform breath alcohol test
- NPI
- SAPS-PD
- CGI-S
- MMSE
- UPDRS II and UPDRS III
- SCOPA-DS
- SCOPA-NS
- RBDQ
- C-SSRS
- Adverse events

11.9.10. Visit 14 (+ 7 days Post Last Dose [± 2 days]); Follow-up

All subjects who complete the study or discontinue early will have a safety follow-up (7 ± 2 days) after their last dose of study drug. The following procedures will be conducted during this visit:

- Concomitant medications
- Physical and neurological examination
- Weight
- Vital sign measurements

- C-SSRS
- Adverse event monitoring

11.9.11. Telephone Contacts

A telephone call to the subject will be made on the first 2 days after initial dosing of DB and OL study drug (Day 1 and Day 43) and after any dose adjustment (increase or decrease) as well as at Study Week 12 and Week 16 (midpoint between Visit 11 and Visit 12, and midpoint between Visit 12 and Visit 13).

The following will be discussed during each telephone contact:

- Prior/concomitant medications
- Adverse events

If subject appears to be symptomatic as assessed by the site during a telephone contact and requires additional assessments in-clinic, an unscheduled visit will be made as early as possible (see Section 11.9.12).

11.9.12. Unscheduled Visit

If subject appears to be symptomatic as assessed by the site during a telephone contact and requires additional assessments in-clinic, an unscheduled visit will be made as early as possible. The following procedures and assessments will be conducted during this visit:

- Prior/concomitant medications
- Physical and neurological examination
- Vital sign measurements (prior to ECG)
- Perform standard 12-lead ECG
- SAPS-PD
- CGI-S
- UPDRS II and UPDRS III
- Blood samples for clinical laboratory evaluation (hematology, serum chemistry, HbA_{1c}, glucose panel, and lipid panel), as needed
- Urine sample for urinalysis, as needed
- Breath alcohol test, as needed
- C-SSRS
- Adverse events
- Study drug accountability, only if dose reduction at unscheduled visit
- Dispense study drug, only if dose reduction at unscheduled visit

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

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

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

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

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. 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

Pretreatment events will be collected and recorded from the time informed consent is provided up to the time of the first dose of study drug administration (ie, at Visit 1 and Visit 2). AEs will be collected and recorded from after first administration of study drug to the last study visit (ie, Visit 2 [postdose] to Visit 13 and unscheduled visits).

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

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

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

The severity of AE:

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

The frequency of AE:

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

The action taken with the study treatment:

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

The outcome of the AE:

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

The causal relationship of the AE to the study treatment:

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

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

12.4. Immediately Reportable Events

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

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after first administration of study drug through 30 days following the last dose of the study drug, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form. In addition, pretreatment events that meet the definition of serious (Section 12.1.2) should be reported following the same guidelines.

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

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

An initial or follow-up SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG within 24 hours of the Investigator or study center staff

becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. PPD-PVG provides the SAE form used to report SAEs.

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

12.4.2. Pregnancy

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

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

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

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

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

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

13.1. Criteria for Study Drug Discontinuation

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

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

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

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

13.2. Clinical Assessments After Study Drug Discontinuation

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

For subjects who have received study drug and who prematurely discontinue from the study treatment (ie, do not complete through Visit 13), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.9.9.

Subjects who receive study drug will complete a follow up visit 7 (± 2) days after the last visit to assess any post study discontinuation adverse effects as described in Section 11.9.10.

14. STUDY TERMINATION

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

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

In the event of study or site termination, subjects will undergo final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.9.4 and safety follow-up visit as described in Section 11.9.10.

15. STATISTICS

15.1. Sample Size

A total of approximately 36 subjects will be randomized in 2:1 ratio to SEP-363856 and placebo, with approximately 24 subjects assigned to SEP-363856 and 12 subjects assigned to placebo. The sample size will provide powers of 59%, 48%, 37%, and 27% to detect treatment effect sizes of 0.8, 0.7, 0.6, and 0.5, respectively, in change from Baseline in SAPS-PD at Week 6 for SEP-363856 versus placebo. It was estimated by using a two independent sample t-test method with 2-sided significant level of 0.05. The sample size was determined for the purposes of exploring the efficacy, safety and tolerability of flexible dosing with SEP-363856 (25, 50, or 75 mg/day) for 6 weeks in male and female subjects with a clinical diagnosis of PDP. A sufficient number of subjects will be enrolled to ensure 36 randomized subjects.

15.2. Analysis Populations

15.2.1. Modified Intention-to-Treat Population

The modified intention-to-treat (mITT) population will consist of all subjects who are randomized, have received at least one dose of study drug, and have a Baseline and at least one post-Baseline efficacy measurement during the DB treatment period. The mITT population will be the primary population for the efficacy analyses. Subjects will be analyzed according to randomised treatment group.

15.2.2. Per Protocol Population

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

- Received assigned study medication as randomized
- Have 14 days or more continuous exposure
- Have 75% - 125% compliance, both limit values inclusive
- Have no major protocol violations, determined by a blinded data review prior to database lock

Selected efficacy endpoints will be analyzed using the PP population.

15.2.3. Safety Population

The safety population will consist of all subjects who are randomized and have received at least one dose of study drug during the DB treatment period. Safety population will be the primary population for the safety analyses. Subjects will be analysed according to the actual treatment received (ie, placebo vs SEP-363856).

15.2.4. OL Extension Safety Population

The OL extension safety population will consist of all subjects who receive at least one dose of study drug during the 12-week open-label extension period. The OL extension safety population will be used for the long-term safety, tolerability, and efficacy analyses. All the by-treatment summaries will be based on the treatment received during the DB period (i.e. SEP-363856 → SEP-363856 vs. Placebo → SEP-363856). Changes from baseline in all safety measures will be summarized at each scheduled post-baseline extension visit, based on both the DB baseline and the OL baseline.

15.3. Data Analysis

15.3.1. Subject Disposition

Subject disposition during the DB treatment period will be summarized by the randomized treatment group (if applicable) and overall for all subjects. The number and percentage of subjects who are screened, screen-failed, randomized, and completed or discontinued the study (including reasons for discontinuation) will be presented.

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

15.3.2. Drug Exposure and Compliance

Drug exposure and compliance will be summarized by treatment for the safety population for the single-blind and double-blind period, and for the OL extension safety population for the open-label extension period.

Drug exposure (in days) will be calculated as: last dose date - first dose date + 1. Exposure will be summarized both as a continuous variable for the single-blind, double-blind period, and OL extension period (ie, mean days), and categorically.

For double-blind:

- Number and percentage of subjects with drug exposure ≥ 4, ≥ 7, ≥ 14, ≥ 21, ≥ 28, ≥ 35 and ≥ 42 days;
- Number and percentage of subjects with drug exposure for 1 - 3, 4 - 6, 7 - 13, 14 - 20, 21 - 27, 28 - 34, 35 - 41 and ≥ 42 days

For OL extension:

- Number and percentage of subjects with extension study drug exposure ≥ 1, ≥ 7, ≥ 14, ≥ 21, ≥ 28, ≥ 56, and ≥ 84 days;
- Number and percentage of subjects with extension study drug exposure for 1 - 6, 7 - 13, 14 - 20, 21 - 27, 28 - 55, 56 - 83, and ≥ 84 days

Percent compliance will be calculated by visit and overall for the double-blind period as: (number of capsules taken / number of capsules should have been taken) × 100%.
Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the

double-blind period. Subjects with missing compliance will not be classified as non-compliant. Compliance will be summarized both as a continuous variable (ie, mean percentage) and categorically (ie, number and percentage of subjects who are compliant vs. non-compliant, or with compliance < 75%, 75% - 125%, > 125%, and missing). Similarly, percent compliance will be calculated, and summarized both as a continuous variable and categorically for the entire open-label extension period.

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

15.3.3. Important Protocol Deviations

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

- Did not meet inclusion/exclusion criteria.
- Received any disallowed concomitant medication.
- Have overall double-blind compliance rate < 75% or > 125%.

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

15.3.4. Demographic and Baseline Characteristics

Basic demographics (eg, age, gender, race, ethnicity, etc.) will be summarized for all screened subjects, by randomization status (ie, randomized vs. not randomized), and for subjects who entered the OL extension period. Demographic and Baseline characteristics will be summarized for the mITT population and safety population, as well as for the OL extension safety population.

Selected data (e.g. weight, BMI, SAPS-PD total score, NPI score, etc.) will be summarized at both the double-blind (DB) baseline and the open-label (OL) baseline of study.

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

15.3.5. Efficacy Analyses

15.3.5.1. Primary Efficacy Endpoint Analysis

This section describes the primary analysis for the primary efficacy endpoint. Sensitivity analysis of this endpoint is described in Section 15.3.12.

The primary efficacy variable is the change from baseline in SAPS-PD score at Week 6 during the DB period for testing superiority of SEP-363856 to placebo. A Mixed Model for Repeated Measures (MMRM) will be used for this comparison. The MMRM model will include factors for treatment, visit (as a categorical variable), and treatment-by-visit interaction, and include baseline SAPS-PD score as a covariate. An unstructured covariance matrix will be used for the within-subject correlation and the Kenward-Rogers approximation will be used to calculate the denominator degree of freedom.

The primary analysis for the primary efficacy endpoint will be based on the observed data only. Missing observations will not be imputed.

15.3.5.2. Secondary Efficacy Endpoint Analysis

CGI-S score

Change from Baseline in CGI-S score at Week 6 during the DB period will be analyzed using an MMRM model similar to that of the primary efficacy variable, with change from Baseline in CGI-S score at each visit as the response variable and Baseline CGI-S score as a covariate.

NPI

Change from Baseline in NPI score at Week 6 during the DB period will be analyzed using an MMRM model similar to that of the primary efficacy variable, with change from Baseline in NPI score at each visit as the response variable and Baseline NPI score as a covariate.

MMSE

Change from Baseline in MMSE score at Week 6 during the DB period will be analyzed using an MMRM model similar to that of the primary efficacy variable, with change from Baseline in MMSE score at each visit as the response variable and Baseline MMSE score as a covariate.

The absolute values of the secondary efficacy measures at both the DB baseline and OL baseline, and at each scheduled post-baseline extension visit, will be summarized descriptively. Changes from baseline in these measures will be summarized at each scheduled post-baseline extension visit, based on both the DB baseline and the OL baseline.

15.3.5.3. Other Efficacy Endpoint Analysis

Data from SCOPA-NS, SCOPA-DS, and UPDRS II and III, will be analyzed similarly.

The total score and change from baseline will be summarized by timepoint for each treatment group. Change from baseline at Week 6 will be analyzed by an analysis of covariance (ANCOVA) model with treatment as a fixed effect, and baseline score as a covariate.

The absolute values of the other efficacy measures at both the DB baseline and OL baseline, and at each scheduled post-baseline extension visit, will be summarized descriptively. Changes from baseline in these measures will be summarized at each scheduled post-baseline extension visit, based on both the DB baseline and the OL baseline.

The absolute values of SAPS-PD score at both the DB baseline and OL baseline, and at each scheduled post-baseline extension visit, will be summarized descriptively. Changes from baseline in SAPS-PD score will be summarized at each scheduled post-baseline extension visit, based on both the DB baseline and the OL baseline.

15.3.5.4. Adjustment for Multiplicity

No multiplicity adjustment will be performed in the testing of the efficacy endpoints.

15.3.5.5. Subgroup Analysis

Exploratory analyses will be performed on certain subgroups of interest for the primary efficacy endpoint of change from Baseline in SAPS-PD score at Week 6 and the secondary endpoint of change from Baseline in CGI-S score at Week 6. The subgroup factors of interest may include: categorized age, gender, and race. Details of the subgroup analyses will be described in the statistical analysis plan (SAP).

15.3.6. Safety Analyses

15.3.6.1. Adverse Events

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

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

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

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

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

The following conventions will be followed in summarizing AEs:

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

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

For the OL extension period, the summary of AEs will be limited to those that occurred on or after the first dose (of the 12-week open-label extension period) of the study drug.

15.3.6.2. Clinical Laboratory Assessments

Clinical laboratory parameters will be summarized by presenting shift tables and by presenting summary statistics for the absolute values as well as the change from Baseline values by treatment. For laboratory parameters with categorical outcomes, the number and percentage of subjects with each outcome will be presented. The data listings will flag values outside the reference range.

For the OL extension period, both the DB baseline and the OL baseline will be used in the calculation of change from baseline values.

15.3.6.3. ECGs/Centrally-read ECG

Absolute values and changes from Baseline in ECG parameters will be summarized by treatment. In addition, the number and percentage of subjects with elevated QTc intervals (QT interval corrected for heart rate) (> 450 msec, > 480 msec, and > 500 msec) and changes in QTc intervals ≥ 30 msec and ≥ 60 msec will be summarized by treatment. Fridericia's correction (QTcF) and Bazett's correction (QTcB) will be used for QT interval correction.

For the OL extension period, both the DB baseline and the OL baseline will be used in the calculation of change from baseline values.

15.3.6.4. Vital Signs

Vital sign parameters, as well as weight and BMI, will be summarized by presenting summary statistics for the absolute values and the change from Baseline values by treatment.

For the OL extension period, both the DB baseline and the OL baseline will be used in the calculation of change from baseline values.

15.3.6.5. Physical/Neurological Examination

All physical and neurological exam findings at screening will be captured in the medical history and summarized together with the other medical history events. Clinically significant changes from the screening visit (including the extension visits) will be captured as AEs as appropriate, and summarized together with the other AEs. Physical and neurological examination findings will also be provided in a data listing.

15.3.6.6. Concomitant Medications

All medications will be coded to indication-specific Anatomical Therapeutic Chemical (ATC) classification (ie, ATC level 3) and preferred name using the WHO-DD.

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

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

15.3.6.7. Suicidality Measure

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

15.3.6.8. Subgroup Analysis

Selected safety data will be presented by demographic subgroups. Details of subgroup analysis of the safety data will be provided in SAP.

15.3.7. Population Pharmacokinetic Analysis

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

15.3.8. Pharmacokinetic/Pharmacodynamic Analysis

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

15.3.9. Pharmacogenomic Analysis

The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on plasma SEP-363856 exposure will be explored; the results of which will be reported separately.

15.3.10. Interim Analysis

No formal interim analysis is planned during double-blind phase. Unblinding will occur after database lock of double-blind phase, and statistical analyses for double-blind phase will be conducted. Full analyses including open-label phase will be conducted after database lock of open-label phase.

15.3.11. Treatment of Missing Data

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

For the MMRM models, no imputation for missing data will be applied unless otherwise specified.

15.3.12. Sensitivity Analyses

This section describes the sensitivity analyses for the efficacy data.

As a supportive analysis for the efficacy endpoints of change from Baseline in SAPS-PD total score or CGI-S score at Week 6, missing data at Week 6 will be imputed using the last observation carried forward (LOCF) method, and the data will be analyzed using an ANCOVA model. The respective response variable for the model will be: change from Baseline in SAPS-PD total score at the Week 6 LOCF endpoint and change from Baseline in CGI-S score at the Week 6 LOCF endpoint. The ANCOVA model will include treatment as fixed factors and include Baseline score as a covariate.

Subjects will be grouped by the visit at which they had their last SAPS-PD total score (or CGI-S score) measured. Mean change from Baseline in SAPS-PD total score and mean change from Baseline in CGI-S score will be plotted by the dropout category and by reason of discontinuation, in order to assess whether these two efficacy measures appear to be correlated with study dropout.

The mechanisms that cause missing data may or may not be at random. The MMRM model used in the primary analysis of the two efficacy endpoints above relies on the assumption of missing at random (MAR). In order to explore the robustness of the primary analyses, sensitivity analyses, such as a random effects pattern mixture model and a pattern mixture model with placebo-based multiple imputation, may be performed for these two efficacy endpoints. Details of these analyses will be provided in the SAP.

No sensitivity analyses are planned for the OL extension period.

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

16.1. Data Collection/Electronic Data Capture (EDC)

For enrolled subjects, the results from Screening and data collected during the study (except clinical laboratory test results) will be recorded in the subject's electronic CRF. Screen failed subjects will have a limited number of required electronic CRFs. Data will be entered into source documents prior to being transcribed into the CRF. This transcribing will be done once a subject has passed screening (Visit 1). The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulations (CFR) Part 11. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator or delegate.

16.2. Computerized Systems Used for Source Data

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

Table 8: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent (subject and caregiver)[a]	A
Obtain informed consent for pharmacogenomics sample collection	A
Review inclusion/exclusion criteria	A
Review randomization criteria	A
Prior/concomitant medication review	A
Randomize (IXRS) to treatment	A, E
Dispense study drug	A, E
Study drug accountability	A, E
Telephone contacts	A
Demography	A
Medical history	A
Psychiatric history/mental status	A
Physical and neurological examination	A

Table 8: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Height	A
Vital signs	A
Weight	A
Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B
Serum prolactin	B
Serum or plasma Glycosylated hemoglobin (HbA_{1c})	B
Serum or plasma Glucose and Lipid panel	B
Thyroid panel (TSH)	B
Coagulation panel (PTT, aPTT, INR)	B
Serum follicle stimulating hormone (FSH)	B
Serum human chorionic gonadotropin (β-hCG)	B
Breath alcohol test	A
Blood sample for pharmacogenomics (CYPP450 2D6)	D
Blood sample for plasma SEP-363856 PK	D
Urine drug screen	B
Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD)	D, F
Clinical Global Impression – Severity (CGI-S)	A
Mini Mental State Exam (MMSE)	A
Scales for Outcomes in Parkinson's Disease Sleep Scale – Daytime Sleepiness (SCOPA-DS)	A
Scales for Outcomes in Parkinson's Disease Sleep Scale – Nighttime Sleep Quality (SCOPA-NS)	A
Unified Parkinson's Disease Rating Scale Parts 2 and 3 (UPDRS II and III)	A
Neuropsychiatric Inventory (NPI)	A
Rapid Eye Movement (REM) Sleep Behavior Disorder questionnaire (RBDQ)	A
Columbia-Suicide Severity Rating Scale (C-SSRS)	A

Table 8: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Pretreatment events	A
Adverse events (AE) monitoring	A
Statistical analysis	SAS®, version 9.2 or higher

A = EDC (MediData RAVE); B = LIMS; C = Core Lab Over-read; D = LIMS/ASCII; E = IXRS, F = Electronic Clinical Outcome Assessments (eCOA).

Abbreviations: EDC = electronic data capture; CDR = clinical data repository; IVRS = interactive voice recognition system; IXRS = interactive response technology; LIMS = laboratory information management system.

[a] Note: Both subject and caregiver informed consent will be collected by the site, but only the subject informed consent will appear in the clinical database.

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

16.4. Audits

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

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

16.5. Study Documentation

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

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

16.6. Clinical Laboratory Certification and Normal Values

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

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

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

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

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

17.2. Institutional Review Board/Independent Ethics Committee

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

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

Before recruitment and enrollment, each prospective subject and caregiver will be given a full explanation of the study, allowed to read the approved informed consent forms 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 and caregiver understands the implications of participating in the study, the prospective subject and caregiver 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 and their caregiver that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study drug, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent forms 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 forms must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form(s) 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(s) must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

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

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

17.5. Protocol Amendments and Emergency Deviations

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

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

17.6. Records Retention

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

17.7. Inspection of Records

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

17.8. Publication Policy

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

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

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

18. REFERENCES

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19. INVESTIGATOR APPROVAL

I have read the protocol, SEP361-203, Version 6.00, "A Multicenter Randomized Double-blind followed by an Open-label Extension Study to Evaluate the Efficacy, Safety, and Tolerability of SEP-363856 in Subjects with Parkinson's Disease Psychosis," and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

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

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

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

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

2. Subject Restrictions and Instructions

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

3. Reporting

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

4. Data Standardization

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

21. APPENDIX II. CLINICAL LABORATORY TESTS

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

Clinical Safety Panel

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

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (CO_2), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Creatine phosphokinase (CPK), Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

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

COAGULATION PANEL: International Normalized Ratio (INR), Partial Thromboplastin Time (PTT), Activated Partial Thromboplastin Time (aPTT)

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

THYROID PANEL: Thyroid stimulating hormone (TSH)

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

OTHER TESTS: Serum Pregnancy (β-hCG) (in female subjects only) Glycosylated hemoglobin (HbA_{1c}), serum follicle stimulating hormone (FSH), prolactin, breath alcohol test

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.

BLOOD SAMPLES FOR PLASMA PHARMACOKINETICS

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

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	Predose (approximately 30 minutes prior to dosing) and 1 sample between 1-3 hours post dose	6 mL each
Day 43	Day 43 (12 ± 4 hours after the Day 42 dose). Actual date and clock time will be recorded.	6 mL
Day 71	Day 71 (12 ± 4 hours after the Day 70 dose). Actual date and clock time will be recorded.	6 mL
Day 127	Day 127 (12 ± 4 hours after the Day 126 dose). Actual date and clock time will be recorded.	6 mL

23. APPENDIX IV. 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).