STATISTICAL ANALYSIS PLAN

CLINICAL STUDY PROTOCOL SEP361-118

AN OPEN-LABEL POSITRON EMISSION TOMOGRAPHY STUDY TO INVESTIGATE THE EFFECT OF ADJUNCTIVE ADMINISTRATION OF SEP-363856 ON BRAIN DOPAMINE SYNTHESIS CAPACITY USING ^{18}F-DOPA IN ADULT SUBJECTS WITH SCHIZOPHRENIA

[redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE-APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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1. INTRODUCTION

Schizophrenia is a chronic and disabling neurodegenerative disorder characterized by a mixture of positive symptoms, negative symptoms, and cognitive deficits. SEP-363856 is currently being investigated in subjects with schizophrenia. One randomized, double-blind study (SEP361-201) evaluating efficacy and safety of flexible SEP-363856 doses (50 mg/day or 75 mg/day) in adult subjects with schizophrenia is clinically complete. Subjects who completed this study are eligible to enroll in a 26-week open-label safety and tolerability study of SEP-363856 (SEP361-202).

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

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

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

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK) data for Protocol SEP361-118. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on Sumitomo Pharma America, Inc. (formerly Sunovion Pharmaceuticals Inc.; herein referred to as SMPA) Protocol version 5.00, dated 18MAR2020.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

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

2.2. SAFETY OBJECTIVES

The safety objectives are:

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

- To assess whether adjunctive administration of SEP-363856 is associated with extrapyramidal symptoms as measured by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS).

2.3. OTHER OBJECTIVES

The other objectives are:

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

3. STUDY ENDPOINT

3.1. PRIMARY ENDPOINT

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

3.2. SAFETY ENDPOINTS

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

3.3. OTHER ENDPOINTS

- Change in baseline resting state BOLD fMRI signal at Week 2.

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

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

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

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

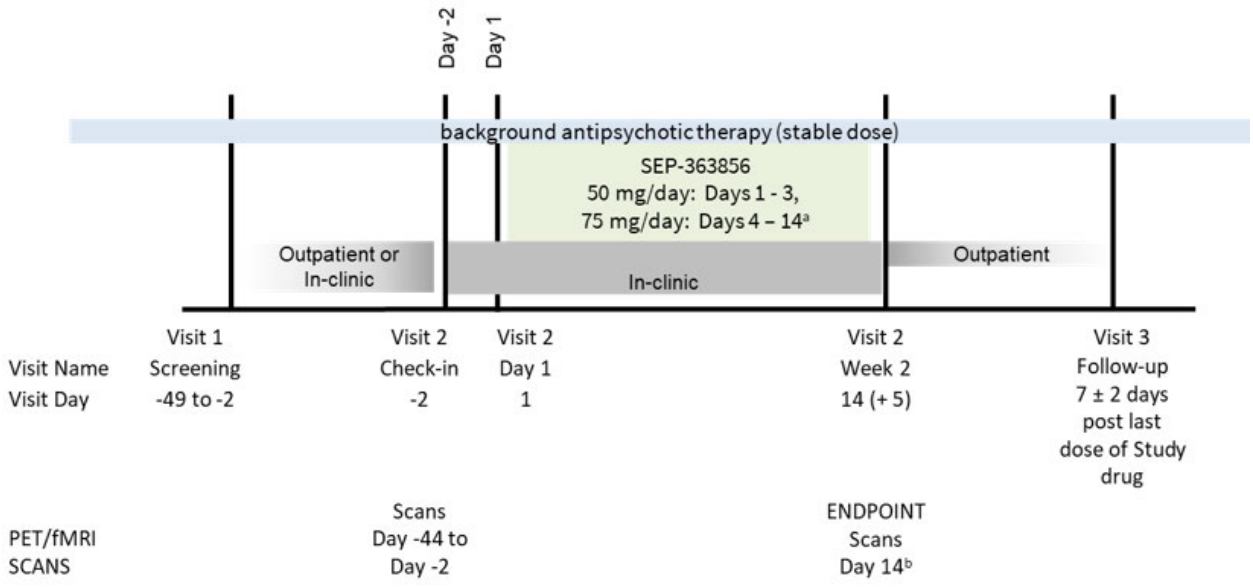
During each PET scan, there will be two periods of resting state fMRI collection, and one period for NM-MRI and iron-sensitive MRI collection. Two PET scans will be conducted during the study: 1 PET scan prior to dosing (between Day -44 to Day -2) and 1 PET scan following approximately 14 days of treatment (Day 14).

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

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

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

Figure 1: Study Schematic



[a] Dose reduction to 50 mg/day allowed for reasons of tolerability.

[b] Subject must remain in-clinic and on treatment until completion of the Visit 2 assessments, including scans. In the event of an unsuccessful PET scan on Day 14, additional days of dosing may be necessary up to, but not exceeding, Day 19

Schedule of Events

Schedule of events can be found in Section 1 Table 2 of the Protocol.

4.2. CHANGES TO ANALYSIS FROM PROTOCOL

No changes to the planned analyses are due to COVID-19.

Protocol:

15.2. Analysis Populations

The Per Protocol Population defined in the Protocol will not be utilized for either safety analysis covered by this SAP or imaging analysis covered by a separate SAP. Therefore, a per protocol population will not be determined for this study.

15.3.3. Important Protocol Deviations

"The number and percentage of subjects with IPDs will be summarized by type of deviation and dose group."

Change to "The number and percentage of subjects with IPDs will be summarized by category of deviation for SEP-363856 (Overall) for the safety population."

15.3.8.2. Clinical Laboratory Assessments

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

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

Change to "For laboratory parameters with continuous outcomes, descriptive statistics (number of subjects, mean, SD, median, Q1, Q3, minimum, and maximum) for the observed values and for changes from baseline will be presented for SEP-363856 (Overall) [which refers to the overall treatment group] at each visit. For laboratory parameters with categorical outcomes, the number and percentage of subjects with each outcome will be presented for SEP-363856 (Overall) at each visit.

The number and percentage of subjects with Sponsor defined potentially clinically significant (PCS) laboratory values (defined in the SAP) will be summarized for SEP-363856 (Overall) at each visit. The data listings for laboratory parameters will flag values outside of the reference range. PCS laboratory findings will be displayed in a separate data listing."

15.3.8.3. Electrocardiograms

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

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

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

- QTcF > 500 ms at any postdose timepoint (including unscheduled visits) and not present at baseline
- QTcF > 480 ms at any postdose timepoint (including unscheduled visits) and not present at baseline
- QTcF > 450 ms at any postdose timepoint (including unscheduled visits) and not present at baseline
- Change from baseline in QTcF ≥ 60 ms for at least one postdose measurement (including unscheduled visits)
- Change from baseline in QTcF ≥ 30 ms for at least one postdose measurement (including unscheduled visits) and < 60 ms for all postdose measurements (including unscheduled visits)"

15.3.8.4. Vital Signs

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

Change to "The number and percentage of subjects with orthostatic hypotension will be summarized by timepoint and for the overall post-dose period for SEP-363856 (Overall). Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after the subject had been standing for at least 2 to 4 minutes, compared to the systolic and diastolic blood pressures measured in the supine position, respectively."

15.3.8.6 Concomitant Medications

Change "Medication taken between screening and the follow-up visit will be reported as concomitant." to "Other than the study drug, any medication taken during the course of the study, with a start date/time on or after the first dose of study drug and on or before the last dose of study drug; or with a start date/time prior to, and an end date/time on or after, the first dose of study drug, or marked as ongoing, will be considered concomitant."

Appendix II Clinical Laboratory Tests

"HEMATOLOGY**:** (Differential reported as % and absolute value)" changed to "HEMATOLOGY: (Differential reported as fraction of 1 and absolute value)".

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

5.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

5.2. INTERIM ANALYSIS

No interim analysis is planned.

5.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP (which does not include PET and fMRI analysis) will be performed by IQVIA Biostatistics following database lock.

6. ANALYSIS POPULATIONS

Enrolled subjects are subjects who signed the ICF and did not screen fail at their final screening.

Three analysis populations will be defined in this study. The population for PET and fMRI analyses will be specified in a separate Statistical Analysis Plan.

6.1. SAFETY POPULATION [SAF]

The safety population will consist of all subjects who receive at least one dose of study drug.

6.2. EFFICACY POPULATION [EFF]

The efficacy population is defined as all subjects who have received at least one dose of study drug and have any postdose data for the PANSS, CGI-S, BNSS or MADRS.

7. STATISTICAL CONSIDERATIONS

7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show the start/ stop day of assessments and events.

Reference start date is defined as the date of the first dose of study medication (Day 1 is the study day of the first dose of study medication).

- If the date of the assessment or event is on or after the reference start date then:

  Study Day = (date of assessment or event – reference start date) + 1.

- If the date of the assessment or event is prior to the reference start date then:

  Study Day = (date of assessment or event – reference start date).

In the situation where the assessment or event date is partial or missing, Study Day and any corresponding durations will appear missing in the listings. Partial assessment or event dates will however be presented as is in the listings.

7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose of study medication (including unscheduled assessments). Whenever available, the time information should be accounted for in the derivation of baseline values. In the case where time is not available and the date of the last non-missing measurement and the date of the first dose of study medication coincide, that measurement will be considered baseline.

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented.

In the case of a retest, the assessment recorded under the planned visit will be used for by-visit summaries, and the assessment(s) recorded under unscheduled visit(s) will be presented in listings only.

Early termination data will be mapped to the next scheduled or planned timepoint where an assessment is expected to be performed as specified by the Schedule of Assessment table in the Protocol for by-visit summaries. This applies to all efficacy, safety, and PK data.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

Unscheduled measurements will not be included in by-visit summaries. Unscheduled measurements collected prior to the first dose of study medication will contribute to the derivation of the baseline value. Unscheduled measurements collected post baseline will contribute to the derivation of potentially clinically significant (PCS) post-baseline value and worst case value where required.

7.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

7.5. STATISTICAL TESTS

The default significance level will be 5%; confidence intervals (CIs) will be 95%. All p-values and CIs will be two-sided, unless otherwise specified in the description of the analyses.

7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

For PK computations, the Percentage Coefficient of Variation (CV%), Geometric Mean (GM), and Percentage Geometric Coefficient of Variation (GCV% or 'Geometric CV%') will be computed as below:

$$CV\% = 100\ \frac{SD}{Mean}$$

$$GM = e^{Mean_{Log}}$$

$$GCV\% = (100)\sqrt{(e^{SD^2_{LOG}}) - 1}$$

Where SD is the sample standard deviation, Mean is the sample mean, $Mean_{Log}$ is the sample mean of the log transformed data, and SD_{Log} is the sample standard deviation of the log transformed data. Note that when the data are lognormally distributed, CV% and GCV% are equal.

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher

7.8. MISSING DATA

No imputation will be performed for missing data.

7.9. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for the analysis defined in this SAP.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects screened will be accounted for in this study.

The number and percentage of subjects screened, screen failed, and enrolled will be summarized for SEP-363856 (Overall) based on the number of all subjects screened. The number and percentage of subjects under each reason for screen failure will be presented based on the number of subjects screened. Number and percentage of subjects completing the study or terminating early will also be summarized (with reasons for early termination), based on the number of enrolled subjects. The number and percentage of subjects included in the safety and efficacy populations will be presented, based on the number of enrolled subjects.

The number of subjects who failed screening due to COVID-19 related reasons and who discontinued early due to COVID-19 related reasons will be summarized in the disposition table. Subjects who failed screening or discontinued due to COVID-19 related AEs are identified by the following AEs with preferred terms (PTs) and codes:

- Coronavirus test positive (PT code = 10070255), or
- Corona virus infection (PT code = 10053983).

Disposition data will be provided in a listing for screen failures and all subjects enrolled.

9.1. IMPORTANT PROTOCOL DEVIATIONS

Important Protocol Deviations (IPDs) will be identified and documented based on a review of data listings and the protocol deviations log.

The IPD categories may include, but may not be limited to:

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

IPDs will be identified for all enrolled subjects and presented in a data listing. The number and percentage of subjects with IPDs will be summarized by category of deviation for SEP-363856 (Overall) for the safety population.

In addition, a listing of all protocol deviations reported by the clinical team during the study, including impact by COVID-19, will be provided for all subjects enrolled.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the safety population and efficacy population. No statistical testing will be carried out for demographic or other baseline characteristics.

The number and percentage of subjects by gender, racial group and ethnicity will be summarized. Age, baseline height, baseline weight, baseline BMI, baseline efficacy parameters (PANSS total score, PANSS subscale scores (positive, negative, and general psychopathology), CGI-S score, BNSS total score, and MADRS total score) and baseline movement disorder measures (AIMS total score, BARS total score, and SAS mean score) will be summarized using descriptive statistics (number of subjects, mean and standard deviation, median, Q1, Q3,

minimum, and maximum).

Individual subject demographics and baseline characteristics will be presented in listings for all subjects enrolled.

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

11. MEDICAL AND PSYCHIATRIC HISTORY

The medical history as well as psychiatric history of subjects will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. The number and percentage of subjects in each SOC and each PT will be summarized for the safety population for SEP-363856 (Overall).

Each subject's medical and psychiatric history will be listed by SOC and PT for all subjects enrolled.

12. PRIOR AND CONCOMITENT MEDICATIONS

Subjects may not take any disallowed prescription or disallowed non-prescription medications, or dietary or herbal supplements, for at least 5 half-lives or 14 days prior to dosing, whichever is longer or anticipate the need for any disallowed medication during their participation in this trial. Concomitant use of CYP2D6 inhibitors is prohibited. Subjects may not use Clozapine for at least 120 days prior to PET scan at screening. Antidepressants, mood stabilizers, or anxiolytics [lorazepam or equivalent at doses above protocol-specified limits] are prohibited concomitant medications. Electroconvulsive therapy is prohibited within 3 months prior to screening and during the study.

Other than the study drug, any medication taken during the course of the study, with a start date/time on or after the first dose of study drug and on or before the last dose of study drug; or with a start date/time prior to, and an end date/time on or after, the first dose of study drug, or marked as ongoing, will be considered concomitant. Medications that stopped prior to the first dose of study drug will not be considered concomitant but prior medications. Post treatment medications are medications which started after the last dose of study drug.

Antipsychotic agents including depot neuroleptics taken within at least 6 months prior to screening, and any other medications taken within at least 3 months prior to screening, through the End of Study visit will be recorded and reported. All medications will be provided in a listing for all subjects enrolled.

All medications will be coded using the World Health Organization Drug Dictionary (WHODRUG version 01MAR2019). The number and percentage of subjects using each prior/concomitant medication will be summarized for safety population for SEP-363856 (Overall) according to the WHODRUG Anatomic Therapeutic Class (ATC) Level III and preferred name. Subjects with multiple uses of a prior/concomitant medication will be counted once for a given ATC class and preferred name.

Similarly, the number and percentage of subjects using background antipsychotics, including typical, atypical, oral and depot antipsychotics, will be summarized for safety population for SEP-363756 (Overall) according to the

WHODRUG Anatomic Therapeutic Class (ATC) Level III and preferred name. Background antipsychotics, including typical, atypical, oral and depot antipsychotics, are identified based on all prior/concomitant medications with "Started prior to study?" = "Yes" and "Ongoing"="Yes". The definitions of those medications are as below:

Category	Definition
Antipsychotics	ATC3 Code = N05A
Typical Antipsychotics	ATC4 Code = N05AA, N05AB, N05AC, N05AD, N05AF or N05AG
Atypical Antipsychotics	ATC4 Code = N05AE, N05AH, N05AL or N05AX
Oral Antipsychotics	ATC3 Code = N05A and "Route" = "oral"
Depot Antipsychotics	ATC3 Code = N05A and ("Route" = "intramuscular", "subcutaneous" or "other") and ("Frequency" = "As needed" or "other")

13. STUDY MEDICATION EXPOSURE

The total number of days of exposure to study drug by dose level and for SEP-363856 (Overall) will be summarized categorically (N [%]) for the safety population. The total number of doses of exposure to radiotracer will be summarized categorically (N [%]) for the safety population as well.

A data listing, by subject, containing the study medication dosing data will be provided for all subjects enrolled.

14. STUDY MEDICATION COMPLIANCE

Treatment compliance will not be summarized as all dosing will occur in-clinic.

15. EFFICACY OUTCOMES

The analyses of the efficacy variables will be performed on the efficacy population, unless otherwise specified.

15.1. EFFICACY VARIABLES

Efficacy parameters include PANSS total score, PANSS subscale scores (positive, negative, and general psychopathology), PANSS factor scores (Marder factor scores and UPSM factor scores), CGI-S score, BNSS total score, BNSS subscale scores and MADRS total score. Tabular summaries will be based on the Efficacy Population.

The actual values and changes from baseline at each post-dose time point will be summarized, with 95% confidence intervals.

Efficacy parameters for each individual subject will be listed for all enrolled subjects.

PANSS

PANSS is used to measure the psychopathology in adults with psychotic disorders, comprising 30 items and 3 subscales. The positive subscale assesses hallucinations, delusions and related symptoms (7 items), the negative subscale assesses emotional withdrawal, lack of motivation and related symptoms (7 items), and the general psychopathology subscale assesses other symptoms such as anxiety, somatic concern and disorientation (16 items). An anchored Likert scale from 1 to 7 (1 = absent, 7 = extreme, with values of 2 and above indicating the presence of progressively more severe symptoms) is used to score each item. Individual items are summed to derive the following scores:

- Total score = sum of all 30 items. Total score ranges from 30 to 210.
- Subscale scores = sum of items within each of the following subscales:
  - Positive subscale: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility. This subscale score ranges from 7 to 49.
  - Negative subscale: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. This subscale score ranges from 7 to 49.
  - General psychopathology subscale: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance. This subscale score ranges from 16 to 112.
- Marder factor scores – sum of items within each of the following factors (Marder, Davis, Chouinard. 1997):
  - Negative symptoms: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, motor retardation, active social avoidance
  - Positive symptoms: delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution, stereotyped thinking, somatic concern, unusual thought content, lack of judgment and insight

- Disorganized thought: conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, disorientation, poor attention, disturbance of volition, preoccupation
- Uncontrolled hostility/excitement: excitement, hostility, uncooperativeness, poor impulse control
- Anxiety/depression: anxiety, guilt feelings, tension, depression

- UPSM factor scores

  The PANSS item scores of each subject at each visit will be transformed using the uncorrelated PANSS score matrix (UPSM), to obtain the scores of 7 transformed PANSS factors (Hopkins et al. 2018):
  - POS: Positive
  - DIS: Disorganized
  - NAA: Negative apathy/avolition
  - NDE: Negative deficit of expression
  - HOS: Hostility
  - ANX: Anxiety
  - DEP: Depression

  The transformation will be done as follows:

$$[\text{PANSS Data}]_{(N\times 30)} * [\text{UPSM}]_{(30\times 7)} = [\text{Transformed PANSS Factor Data}]_{(N\times 7)}$$

  where

  $[\text{PANSS Data}]_{(N\times 30)}$ is matrix with N PANSS assessments and 30 columns containing the scores of 30 PANSS items ordered in the same way as shown in UPSM.

  $[UPSM]_{(30\times 7)}$ is a matrix with 30 rows (one for each PANSS item) and 7 columns (one for each of the 7 transformed PANSS factors). This matrix is presented in Table 1.

  $[\text{Transformed PANSS Factor Data}]_{(N\times 7)}$ is the transformed matrix with N sets of scores for the 7 transformed PANSS factors

Table 1 - Uncorrelated PANSS Score Matrix (UPSM) for Generating Transformed PANSS Factor Scores

PANSS	UPSM-POS	UPSM-DIS	UPSM-NAA	UPSM-NDE	UPSM-HOS	UPSM-ANX	UPSM-DEP
PANSS01	0.5792730597	-0.1547126840	-0.0828932650	0.0071927220	-0.0593031510	-0.0735449620	0.0020484408
PANSS02	0.0292444390	0.1975824582	-0.0260173260	-0.0234753800	-0.0368756010	-0.0012396240	-0.0361645050
PANSS03	0.2065788330	-0.0179419820	-0.0250663450	-0.0133031880	-0.0300507070	0.0001506005	0.0293001724
PANSS04	-0.0336790630	0.0115284348	0.0011652392	-0.0723891460	0.1379358628	0.1108194656	-0.1045224460
PANSS05	-0.0341508580	-0.0301875430	-0.0041019560	-0.0233459100	-0.0069204000	-0.0313277060	0.0308288417
PANSS06	0.3537254634	-0.0626270750	0.0477329954	0.0012126712	0.0192067437	-0.0161398140	0.0063264235
PANSS07	-0.0383468990	-0.1767919370	-0.0299340700	0.0314652864	0.5025411101	-0.0997121200	0.0573604084
PANSS08	-0.0054230270	-0.0291400280	0.0568702938	0.2474176209	-0.0388464000	0.0188235393	-0.0091524870
PANSS09	-0.0315765690	-0.0243925850	0.3317907576	-0.0228204580	-0.0507096280	-0.0145653830	0.0112689069
PANSS10	-0.0742072890	-0.0401313020	-0.0097485120	0.0161513666	0.0245536353	-0.0176161520	-0.0172218040
PANSS11	-0.0943532590	-0.0856364190	0.4611503804	-0.0286825100	-0.0189062390	-0.0185825180	-0.0130433890
PANSS12	0.0043338689	0.1062496353	0.0255910591	-0.0301470410	-0.0133497570	0.0096065791	-0.0686802390
PANSS13	0.0041274699	0.0051521898	0.0009558861	0.2576813501	-0.0085004640	0.0194235006	-0.1037459520
PANSS14	-0.0111267300	0.1462268689	-0.0276416260	0.0023017188	-0.0055291270	-0.0118427800	0.0040128786
PANSS15	-0.0356272010	0.0552508287	-0.0382627720	0.0110152489	-0.0309176290	0.0444944076	0.1059845189
PANSS16	-0.0331052830	-0.0821894470	-0.0327376640	-0.0533178140	-0.0386473380	0.4576579818	0.1197800301
PANSS17	-0.0368854600	-0.0004363100	-0.0020681500	-0.0407976460	-0.0272172130	-0.0253163640	0.2459654614
PANSS18	-0.0931367690	-0.0332617600	-0.0132943930	0.0231904701	-0.0287529750	0.5123850161	-0.0312522560
PANSS19	-0.0455199430	0.0494113554	-0.0324174560	0.1026255664	-0.0136676190	0.0293507269	-0.0441735260
PANSS20	-0.0344751890	-0.0688197670	-0.0412738350	0.0381793764	0.0042219619	-0.0635101090	0.4514426846
PANSS21	-0.0348890020	-0.0366137810	-0.0779782830	0.4409895205	-0.0073240410	-0.0192655290	0.0464131877

PANSS22	-0.0803690920	0.0334025939	-0.0088488890	-0.0200483170	0.2858700784	-0.0567167860	-0.0531076130
PANSS23	0.1428966744	0.0939213700	-0.0326143600	-0.0367524640	-0.0675856980	-0.0209072840	-0.0177890070
PANSS24	-0.0383047770	-0.0324584080	-0.0255393890	-0.0180115340	-0.0266180700	-0.0210068530	-0.0176029110
PANSS25	-0.1036311520	0.2814367260	-0.0478918640	0.0029986238	0.0037656449	-0.0226520240	0.0401351054
PANSS26	0.0142987589	0.1548635741	-0.0306089330	-0.0331581690	0.0262295986	-0.0576293550	-0.0626180490
PANSS27	-0.0573513270	0.1867914227	-0.0143489160	0.0581534153	-0.0145494330	-0.0371788310	0.0455412078
PANSS28	-0.0748387810	0.0166272025	-0.0267498020	-0.0031632780	0.2546669938	-0.0201249190	-0.0076420280
PANSS29	-0.0520812460	0.2912295497	0.0029775475	-0.0324350460	-0.0442337350	-0.0047991290	0.0567191230
PANSS30	-0.0112030990	-0.0007246980	0.2860136812	-0.0606201430	0.0183598393	-0.0302347770	0.0370748725

CGI-S

The CGI-S is a clinician-rated assessment of the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity. The CGI-S score takes one of the following values: 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), 7 (among the most extremely ill patients).

BNSS

The BNSS is a rating scale to measure the current level of severity of negative symptoms in schizophrenia and schizoaffective disorder. The measure is comprised of 13 individual items organized in 6 subscales (blunted affect (items 9, 10, 11), alogia (items 12, 13), avolition (items 7, 8), anhedonia (items 1, 2, 3), asociality (items 5, 6), and distress (item 4)). The 13 individual items provide a composite total score (ranging from 0 to 78). Each of the items is scored on a Likert-type 7-point scale from 0 - 6, where a value of 0 indicates symptom is absent and a value of 6 means the symptom is a severe form. In addition, BNSS subscale scores will be calculated by summing the item scores under each subscale.

MADRS

The MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. MADRS total score will be calculated by the sum of all 10 item scores.

15.2. MISSING DATA METHOD FOR EFFICACY VARIABLES

The PANSS total score, PANSS subscale scores (positive, negative, and general psychopathology), PANSS factor scores (Marder factor scores and UPSM factor scores), BNSS total score, BNSS subscale scores and MADRS total score will be set to missing if any one item contributing to the total/subscale/factor score is missing. The change from baseline in PANSS total score, PANSS subscale scores (positive, negative, and general psychopathology), PANSS factor scores (Marder factor scores and UPSM factor scores), CGI-S score, BNSS total score, BNSS subscale scores and MADRS total score at Week 2 (Day 14 or ET), will be set to missing if such scores at baseline or at Week 2 (Day 14 or ET) is missing. Missing data will not be imputed.

16. SAFETY OUTCOMES

All tabular summaries for safety outcomes will be based on the safety population.

16.1. ADVERSE EVENTS

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease

occurring after signing the informed consent form (ICF), whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from the time of signing the ICF to the last study visit/EOS visit.

TEAEs are untoward medical occurrences:

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

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

- All TEAEs (including number of events and subject incidence).
- TEAEs by severity (mild, moderate, severe).
- TEAEs by relationship to the study treatment (related, or not related).
- TEAEs by dose at onset (including number of events and subject incidence)
- TEAEs leading to study medication discontinuation (including number of events and subject incidence)
- Serious TEAEs (including number of events and subject incidence)
- TEAEs leading to study discontinuation (including number of events and subject incidence)

The following conventions will be followed in summarizing TEAEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- If a subject reports more than one TEAE within a preferred term and/or a body system, the adverse event with the highest known severity within each body system and within each preferred term will be included in the summaries by severity. Any TEAE with a missing severity will be treated as "severe" and counted in the severe category.
- For summaries by relationship to study drug, TEAEs assessed as "possible," "probable," or "definite" will be grouped as "related." If a subject reports more than one TEAE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related. Any TEAE with a missing relationship to study medication will be regarded as "related" to study medication.
- For summaries by dose at AE onset, TEAEs will be summarized by the last actual dose level the subject was on before the onset of event. If a subject reports more than one TEAE within the same dose level, SOC and PT, it will be counted only once.

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

A listing of AEs (TEAEs and pre-treatment events), as well as a listing of Serious TEAEs, TEAEs leading to discontinuation of study medication and discontinuation from study, TEAEs of potential drug abuse and dependence (see APPENDIX 6), and a listing of treatment emergent deaths will be presented.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to determine whether an AE began before or after dosing, the AE will be classified by the worst case; i.e. treatment emergent.

Presentations regarding each of the categories described in the sub-sections below, will be provided as described and specified in the templates.

16.1.1. ALL AEs

TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) for SEP-363856 (Overall). Listings of pre-treatment events and TEAEs will also be presented for all subjects enrolled. A listing of pre-treatment events will also be presented for screen failures.

TEAEs will also be summarized by SOC, PT and dose at event onset for SEP-363856 (Overall).

16.1.2. AEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

AEs leading to permanent discontinuation of study medication will be identified by using the AE page of the electronic case report form [eCRF], where "Action Taken with Study Treatment" is answered as "Drug Withdrawn". TEAEs will be summarized by SOC and PT for SEP-363856 (Overall). A listing of TEAEs leading to permanent discontinuation of study medication will be presented for all subjects enrolled.

16.1.3. AEs LEADING TO DISCONTINUATION FROM STUDY

AEs leading to permanent discontinuation from the study will be identified by using the AE page of the electronic case report form [eCRF], where "Caused Study Discontinuation" is answered as "Yes". TEAEs will be summarized by SOC and PT for SEP-363856 (Overall). A listing of TEAEs leading to permanent discontinuation from the study will be presented for all subjects enrolled.

16.1.4. SEVERITY OF AEs

Severity is classed as mild/moderate/severe (increasing severity). AEs with a missing severity will be classified as severe. If a subject reports an AE more than once within a SOC/ PT, the AE with the worst case severity (i.e., maximum severity) will be used in the summary.

TEAEs by severity will be summarized by SOC and PT for SEP-363856 (Overall).

16.1.5. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator, is classed as not related, possible, probable, or definite (increasing strength of relationship). A related AE is defined as an AE with a relationship to study medication as possible or probable or definite. AEs with a missing relationship to study medication will be regarded as related to study medication. If a subject reports an AE more than once within a SOC/ PT, the AE with the strongest relationship to study medication will be used in the summary.

TEAEs by relationship to study medication will be summarized by SOC and PT for SEP-363856 (Overall).

16.1.6. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. Serious TEAEs will be summarized by SOC and PT for SEP-363856 (Overall). A listing of serious TEAEs will be presented for all subjects enrolled.

16.1.7. ADVERSE EVENTS LEADING TO DEATH

AEs leading to death are those events which are recorded with an AE outcome of "Fatal" on the Adverse Events page of the (e)CRF. A listing of TEAEs leading to death will be presented for all subjects enrolled.

16.1.8. ADVERSE EVENTS OF POTENTIAL DRUG ABUSE AND DEPENDENCE

AEs of potential drug abuse and dependence are defined as the following PT: All PTs within the FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (CDER 2017), all PTs listed in the MedDRA version 22.0 broad SMQ for Drug abuse and dependence [20000101], and all Pts listed in the FDA FMQ: Study Agent Abuse Potential, Broad (2022). The list of such PTs are found in APPENDIX 6. A listing of TEAEs of potential drug abuse and dependence will be presented for all subjects enrolled.

16.2. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for hematology, serum chemistry, urinalysis, lipid panel, thyroid panel, urine drug screening, serology panel (hepatitis B Ag, hepatitis C Ab, and HIV Ab), coagulation panel and other tests [Serum Pregnancy (β-hCG) (in female subjects only), urine pregnancy test (in female subjects only), follicle stimulating hormone (FSH) (in female subjects only)]. A list of laboratory assessments to be included in the tables and listings is included in 0.

Hematology, serum chemistry (except HbA1c), urinalysis, and lipid panel laboratory tests data are collected at Visit 1 (screening), Visit 2 (Day -2), Visit 2 (Week 2), Visit 3 (follow-up) and ET (early termination). Urine drug screening is performed at Visit 1(screening), Visit 2 (Day -2), Visit 2 (Day 1), Visit 2 (Week 2), Visit 3 (follow-up) and ET (early termination). Serology panel, thyroid panel, HbA1c, and coagulation panel are collected at screening only.

Presentations will use standard international (SI) Units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries and listings will be provided for laboratory data:

- For laboratory parameters with continuous outcomes (serum chemistry, hematology, urinalysis and lipid panel), descriptive statistics (number of subjects, mean, standard deviation, median, Q1, Q3, minimum, and maximum) for the actual values and for changes from baseline (when post-baseline assessments are scheduled) will be presented at each scheduled timepoint for SEP-363856 (Overall). For thyroid panel and coagulation panel, descriptive statistics (number of subjects, mean, standard deviation, median, Q1, Q3,

minimum, and maximum) for the actual values will be presented at each scheduled timepoint for SEP-363856 (Overall). Glucose and lipid panel results will be summarized separately by fasting status: fasting only and overall (fasting, non-fasting, or fasting status unknown combined). Change from baseline for glucose and lipid panel results will only be calculated if post-baseline fasting status is matching baseline fasting status.

- For laboratory parameters with categorical outcomes (urinalysis and urine drug screening), the number and percentage of subjects with each outcome will be presented at each scheduled timepoint for SEP-363856 (Overall).
- Shift in lab results (serum chemistry (except HbA1c), hematology, urinalysis and lipid panel) from baseline to each post-baseline visit according to the reference range criteria provided by the local laboratory.
- The number and percentage of subjects with Sponsor-defined potentially clinically significant (PCS) laboratory values (serum chemistry, hematology, urinalysis and lipid panel) will be summarized for SEP-363856 (Overall) at each visit and overall post-baseline. For the individual visits, percentages will be calculated based on the number of safety population subjects with data available for the given parameter and at the given visit. For the overall post-baseline period, percentages will be calculated based on the number of safety population subjects who had at least one non-missing post treatment test results for a particular laboratory parameter. Any early termination visit, follow-up visit or unscheduled visit that occurs after first dose will be included in the period of evaluation for PCS post-baseline.

Data listings for all laboratory parameters (serum chemistry, hematology, urinalysis, lipid panel, thyroid panel, urine drug screening, serology panel, coagulation panel and other tests) will be provided for all subjects enrolled. Results outside of the reference range will be flagged.

A listing of Potentially Clinically Significant (PCS) laboratory findings (serum chemistry, hematology, urinalysis, lipid panel, thyroid panel and coagulation panel) will be presented for all laboratory parameters with PCS criteria defined for all subjects enrolled.

16.2.1. Laboratory Reference Ranges and Potentially Clinically Significant Criteria

Laboratory reference range indicators provided by the local lab will be used in statistical analyses. Only if a reference range indicator is missing in the data transfer will it be derived in the analysis step as described below.

- Quantitative laboratory measurements (that are not urinalysis erythrocytes or urinalysis leukocytes) will be compared with the relevant laboratory reference ranges in original units and categorized as:
  - Low: Below the lower limit of the laboratory reference range.
  - Normal: Within the laboratory reference range (upper and lower limit included).
  - High: Above the upper limit of the laboratory reference range.
- For qualitative laboratory measurements as well as urinalysis erythrocytes and urinalysis leukocytes, if the result is within the reference range, the indicator is “NORMAL”; if the result is not within range, the indicator is “ABNORMAL”.

In addition, PCS laboratory values will also be identified in accordance with the Sponsor defined PCS criteria as presented in APPENDIX 4.

16.3. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Duration (msec)
- QRS Axis (deg)
- RR interval (msec).
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- HR (bpm)
- Overall assessment of ECG as determined by central over-read:
  - Normal
  - Abnormal, Insignificant
  - Abnormal, Significant
  - Not Evaluable
- ECG findings

Electrocardiogram parameters and changes in these parameters from baseline, as determined by the central over-read, will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, Q1, Q3, minimum, and maximum) at each timepoint for SEP-363856 (Overall) for the safety population. For overall assessment, the number and percentage of subjects will be presented at each timepoint for SEP-363856 (Overall) for the safety population.

Shift in ECG overall assessments from baseline to each post-baseline visit will also be presented.

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

- QTcF/QTcB > 500 ms at any postdose timepoint (including unscheduled visits) not present at baseline
- QTcF/QTcB > 480 ms at any postdose timepoint (including unscheduled visits) not present at baseline
- QTcF/QTcB > 450 ms at any postdose timepoint (including unscheduled visits) not present at baseline
- Change from baseline in QTcF/QTcB ≥ 60 ms for at least one postdose measurement (including unscheduled visits)
- Change from baseline in QTcF/QTcB ≥ 30 ms for at least one postdose measurement (including unscheduled visits) and < 60 ms for all postdose measurements (including unscheduled visits)

For the post-baseline summaries, the percent of subjects will be based on the number of safety population subjects with at least one non-missing post treatment value. For the change from baseline summaries, percentages will be based on the number of subjects with both baseline and at least one post-baseline result available. Any early termination visit, follow-up visit or unscheduled ECG that occurs after first dose will be included for these post treatment summaries.

Data listings for all ECG parameters will be provided for all subjects enrolled.

16.4. VITAL SIGNS

Vital sign data is collected at Visit 1 (Screening), Visit 2 (Day -2), Visit 2 (Day -1), Visit 2 (Day 1 – predose), Visit 2 (Week 2), Visit 3 (follow-up) and ET (Early termination). Weight is collected at Visit 1 (Screening), Visit 2 (Day -2), Visit 2 (Day 1 – predose), Visit 2 (Week 2), Visit 3 (follow-up) and ET (Early Termination). Height and BMI are collected at Visit 1 (Screening) only. Baseline height will be reported with demographics.

The following Vital Signs measurements will be reported for this study:

- Standing/ Supine Systolic Blood Pressure (mmHg)
- Standing/ Supine Diastolic Blood Pressure (mmHg)
- Standing/ Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Oral Body Temperature (^{0}C)
- Weight (kg)
- BMI (kg/m^2)

These vital signs will be summarized using descriptive statistics at each time point for SEP-363856 (Overall). Changes from baseline will be summarized in the same manner. The number and percentage of subjects with Sponsor defined PCS vital sign values (defined in the Section 16.4.1) will be presented for SEP-363856 (Overall) at each visit and for the overall post baseline period. For the individual visits, percentages will be calculated based on the number of safety population subjects with data available for the given parameter and time point. For the overall post-baseline period, percentages will be calculated based on the number of safety population subjects who had at least one non-missing post treatment test result for a particular parameter. Any early termination visit, follow-up visit or unscheduled visit that occurs after first dose will be included in the period of evaluation for PCS post-baseline.

The following summaries and listings will be provided for vital signs data:

- Actual value and change from baseline presented at each time point for SEP-363856 (Overall)
- Incidence of PCS values presented for SEP-363856 (Overall)
- Listing of vital signs data for all enrolled subjects.
- Listing of vital signs data meeting PCS criteria for all enrolled subjects

- The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized for SEP-363856 (Overall), by time point and for the overall post-baseline period. Orthostatic hypotension and orthostatic tachycardia are defined in Section 16.4.2.

16.4.1. VITAL SIGNS POTENTIALLY CLINICALLY SIGNIFICANT (PCS) CRITERIA

Potentially clinically significant vital signs measurements will be identified in accordance with the following predefined PCS criteria:

Parameter Name	PCS Low	PCS High
Standing/ Supine Systolic Blood Pressure (mmHg)	Value ≤ 90 and ≥ 20 decrease from baseline	Value ≥ 180 and ≥ 20 increase from baseline
Standing/ Supine Diastolic Blood Pressure (mmHg)	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 105 and ≥ 15 increase from baseline
Standing/ Supine Pulse Rate (beats/min)	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 120 and ≥ 15 increase from baseline
Weight (kg)	≥ 7% decrease from baseline	≥ 7% increase from baseline
Temperature (°C)	NA	Value ≥ 38.3°C and ≥ 0.8°C increase from baseline

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16.4.2. ORTHOSTATIC EFFECTS

Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after the subject had been standing for at least 2 to 4 minutes, compared to the systolic and diastolic blood pressures measured in the supine position, respectively.

Orthostatic tachycardia is defined as a heart rate increase of >= 20 beats per minute (bpm) and a heart rate of >100 bpm after the subject had been standing for at least 2 to 4 minutes, compared to the heart rate measured in the supine position.

The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized at each scheduled timepoint and for the overall post-baseline period for SEP-363856 (Overall). Any early termination visit, follow-up visit or unscheduled visit that occurs after first dose will be included in the period of evaluation for overall post-baseline incidence summary. For orthostatic hypotension, percentages will be calculated based on the number of safety population subjects who were assessed for both supine and standing blood pressure at the given timepoint. For orthostatic tachycardia, percentages will be calculated based on the number of safety population subjects who were assessed for both supine and standing heart rate at the given timepoint. For overall post-baseline incidence summary, if a subject experienced more than 1 episode of orthostatic hypotension/tachycardia, the subject was counted only once for the corresponding parameter. Systolic and diastolic BP values showing orthostatic hypotension will be flagged in the listing of vital signs data. Heart rate values showing orthostatic tachycardia will be flagged in the listing of vital signs data.

16.5. PHYSICAL AND NEUROLOGICAL EXAMINATIONS

Findings from the physical examination will be presented as follows:

Pre-existing clinically significant conditions recorded as medical history (at screening). Refer to Section 11 for data display of medical history.

New clinically significant conditions recorded as AEs (post baseline). Refer to Section 16.1 for data display of AEs.

16.6. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal behavior and suicidal ideation for lifetime, one month prior to the screening visit, and throughout the study. 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 C-SSRS Baseline/Screening Version is used at the screening visit and the C-SSRS Since Last Visit Version is used from Visit 2 onward. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional.

C-SSRS includes four sections: Suicidal Ideation, Intensity of Ideation, Suicidal Behavior, and Answer for Actual Suicide Attempts.

C-SSRS Categories

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the C-SSRS endpoints, and to provide clarity in the presentation of the results.

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

The categories of the C-SSRS are not mutually exclusive. Subjects will be counted in each category for which they have an event.

Self-injurious behavior without suicidal intent is a non-suicide-related C-SSRS outcome, and also has a binary response (yes/no).

C-SSRS Analyses

For the purpose of C-SSRS analysis, "baseline" and "post-baseline" are defined as follows.

Time point	Study Visit	C-SSRS Version	Derivation Rule
Baseline	Screening	Baseline/Screening – Past 1 Month	Most severe outcome
	Day -1	Since Last Visit	
Post-baseline	All post-baseline visits up to and including Week 3/Follow-up/End of Study, including unscheduled visits	Since Last Visit	Most severe outcome

C-SSRS composite endpoints will be derived for each time point of interest (i.e. baseline, post baseline, and each study visit) as follows:

- Any suicidal ideation: A "yes" answer to any one of the 5 suicidal ideation questions on C-SSRS (Categories 1-5).
- Any suicidal behavior: A "yes" answer to any one of the 5 suicidal behavior questions on the C-SSRS (Categories 6-10).
- Any suicidality: A "yes" answer to any one of the 10 suicidal ideation and/or behavior questions on the C-SSRS (Categories 1-10).

For each subject, the suicidal ideation score at each time point of interest (i.e. baseline, post baseline, each study visit) is defined as the maximum suicidal ideation category (1-5) present for the time of interest. If no ideation is present a score of 0 is assigned. A suicidal ideation score of 4 or 5 is considered serious.

The number and percentage of subjects with any suicidality, any suicidal ideation and subtypes of ideation, any suicidal behavior and subtypes of behavior, and any non-suicidal self-injurious behavior will be presented for:

- Baseline (as defined above)
- Post-baseline (as defined above)
- Each scheduled study visit: Screening (Lifetime; Past 1 Month), Day -1, Week 2, Week 3 (Follow-up)

Shift in suicidal ideation score from baseline to the post-baseline time point and to each of the following study visits will be presented: Week 2, Week 3 (Follow-up)

Intensity of ideation for the most severe ideation subtype is measured in terms of frequency, duration, controllability, deterrents, and reasons for ideation. Each is measured with responses ranging from 1 to 5 for frequency and duration, and from 0 to 5 for controllability, deterrents, and reasons for ideation. The ideation intensity total score is the sum of responses to the five items and can range from 2 to 25 for subjects with endorsed suicidal ideation. For subjects with endorsed suicidal ideation, if one or more of these five items are missing at an assessment, the total score will be set to missing. If a subject did not endorse any suicidal ideation, a score of 0 for the ideation intensity total score will be given.

Actual lethality associated with actual attempts is rated on a 6-point scale from 0 = 'No physical damage or very minor physical damage' to 5 = 'Death'. Potential lethality of actual attempts (if actual lethality = 0) is rated on a 3-

point scale from 0 = 'Behavior not likely to result in injury' to 2 = 'Behavior likely to result in death despite available medical care.

All C-SSRS responses will be listed for all subjects enrolled. The ideation intensity total score and the actual lethality and potential lethality of actual attempts will only be presented in data listings.

16.7. MOVEMENT DISORDER MEASURES

Movement disorder measures include AIMS, BARS, and SAS. The BARS, AIMS, and SAS will be summarized descriptively by presenting summary statistics of actual values and change from baseline values. All data from the three scales will be presented in the data listings for all subjects enrolled.

Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk. There are two items related to dental status, as well as three global impression items assessing overall severity, incapacitation, and the subject's awareness of abnormal movements (Guy-1976; Munetz-1988). AIMS total score will be calculated as the sum of items 1 through 7 (ranging from 0 to 28). If any item score contributing to the calculation of AIMS total score is missing, the total score will be set to missing. Items 8 through 12 will not be used in total score calculation. The global severity score (item 8) will be summarized separately.

AIMS total score (observed value and change from baseline) will be summarized numerically by visit. In addition, the AIMS total score at each visit will be classified as "abnormal" if: either at least two items (out of items 1 - 7) have a response of "mild" or higher, or at least one item (out of items 1 - 7) has a response of "moderate" or higher. Otherwise, the non-missing total score will be classified as "normal". This is a modification of the Schooler-Kane criteria for tardive dyskinesia. Shifts from baseline in AIMS total score classification will be summarized by visit and for the overall post-baseline period. Any early termination visit, follow-up visit or unscheduled visit that occurs after first dose will be included in the overall post-baseline period.

The AIMS global severity score will be summarized both numerically and categorically by visit.

The post-baseline AIMS global severity assessment will be classified as "worsened" (score is higher than baseline), "unchanged" (score is equal to baseline), or "improved" (score is lower than baseline), relative to a subject's baseline response. These post-baseline changes will be summarized by visit.

Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale geared toward assessment of neuroleptic-induced akathisia, though it can be used to measure akathisia associated with other drugs as well. The BARS consists of four items, including one item assessing objective restlessness, two items targeting subjective restlessness (awareness and related distress), and one global clinical assessment item. All items are anchored and utilize a 4-point scale, except for the global rating which has a 6-point scale (from absence of akathisia through severe akathisia). The subjective and objective items are summed to yield a total score (ranging from 0 to 9). If any item score contributing to the calculation of BARS total

score is missing, the total score will be set to missing.

BARS total score (observed value and change from baseline) will be summarized numerically by visit. In addition, the BARS item scores for the four items will be summarized both numerically and categorically by visit.

The post-baseline BARS global clinical assessment of akathisia will be classified as "worsened" (score is higher than baseline), "unchanged" (score is equal to baseline), or "improved" (score is lower than baseline), relative to a subject's baseline response. These post-baseline changes will be summarized by visit.

Simpson-Angus Scale (SAS)

The SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale of severity, and address rigidity, gait (bradykinesia), tremor, akathisia, shoulder shaking, glabellar tap, and salivation (Siddiqui-2009; Simpson-1970). SAS mean score is calculated as the average of all 10 item scores. If any item score is missing, the mean score will be set to missing.

SAS mean score (observed value and change from baseline) will be summarized numerically by visit. In addition, SAS mean score at each visit will be classified as "abnormal" if it exceeds 0.3. Otherwise, non-missing mean scores will be classified as "normal". Shifts from baseline in SAS mean score classification will be summarized by visit and for the overall post-baseline period. Any early termination visit, follow-up visit or unscheduled visit that occurs after first dose will be included in the overall post-baseline period.

16.8. SUBGROUP ANALYSIS

No subgroup analyses are planned for the safety parameters.

16.9. PHARMACOKINETIC ANALYSIS

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

Plasma SEP-363856 and SEP-363854 concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. However, if there is at least one BLQ value for a time point, the geometric mean and geometric coefficient of variation% will not be calculated for that time point. Missing concentrations will not be imputed.

Descriptive statistics (n, mean, standard deviation, CV%, geometric mean, geometric coefficient of variation% [GCV%], median, minimum, maximum) will be used to summarize plasma SEP-363856 and SEP-363854 concentration data.

A subject listing of all plasma concentration-time data for SEP-363856 and SEP-363854 will be presented for all subjects enrolled.

16.10. INTERIM ANALYSIS

No interim analysis is planned.

17. REFERENCES

1. Sunovion SEP-363856 Clinical Study Protocol SEP3611-118

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

4. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York, NY: Marcel Dekker, Inc.; 1982.

5. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–46.

6. Hopkins SC, Ogirala A, Loebel A, Koblan KS. Transformed PANSS factors intended to reduce pseudospecificity among symptom domains and enhance understanding of symptom change in antipsychotic-treated patients with schizophrenia. Schizophr Bull 2018;44(3):593-602.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following output conventions:

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order unless shown otherwise in the output templates:

Treatment Group	For Tables and Graphs	For Listings
SEP-363856 (Overall)	SEP-363856 (Overall)	SEP-363856 (Overall)

PRESENTATION OF VISITS

For all outputs, including tables and listings, visits will be represented as follows and in that order unless shown otherwise in the output templates:

Long Name (default)	Short Name
Screening	Scr
Day -2	D-2
Day-1	D-1
Day1	D1
Baseline	BL
Week 2	W2
Week 3/Follow-up/End of Study	W3
Early Termination	ET

Early termination only applies to listings. Unscheduled visits will be presented in listings, if any.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

Subject ID

Date/Time (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

The concept of "date" below should also include time information whenever time is available for both comparators.

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Partial, but known components show that it is on	Known	TEAE
	Partial	TEAE

START DATE	STOP DATE	ACTION
or after study med start date	Missing	TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT / POST-TREATMENT MEDICATIONS:

The concept of "date" below should also include time information whenever time is available for both comparators.

For the case where the medication start date is known and is equal to the end of treatment date, and the medication start time is unknown, or the case where the imputed medication start date is equal to the end of treatment date:

- If CRF question 'Started after last dose of study medication?' = No, then assign as concomitant.
- If CRF question 'Started after last dose of study medication?' = Yes, then assign as post treatment.

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment.
Known	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown). Then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
Known	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date: CRF questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of birth [if full date is available]). • If month and day unknown, impute as the later of (1st January; date of birth [if full date is available]). CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes. • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Partial	Impute start date as earliest possible date: CRF questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of birth [if full date is available]). • If month and day unknown, impute as the later of (1st January; date of birth [if full date is available]). CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes. • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown). Then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Missing	Impute start date as earliest possible date: CRF questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of birth [if full date is available]). • If month and day unknown, impute as the later of (1st January; date of birth [if full date is available]). CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes. • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No. • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = No, assign as concomitant If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = Yes, assign as post treatment.

START DATE	STOP DATE	ACTION
Missing	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown). Then: If stop date < study med start date, assign as prior If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = No, assign as concomitant If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = Yes, assign as post treatment.
Missing	Missing	If CRF question 'Started after last dose of study medication?' = No, assign as concomitant. If CRF question 'Started after last dose of study medication?' = Yes, assign as post treatment.

APPENDIX 3. CLINICAL LABOROTORY PARAMETERS

- **HEMATOLOGY:** (Differential reported as fraction of 1 and absolute value)

  Hemoglobin, Hematocrit, Platelet Count, Red blood cell (RBC) Count, White blood cell (WBC) - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

- **BLOOD CHEMISTRIES:**

  Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), CPK, Creatinine, Glucose, HbA1c, Magnesium (Mg), Phosphorus (P), Potassium (K), Prolactin, Protein (Total), Sodium (Na), Uric Acid

- **URINALYSIS:**

  Blood, Glucose, Ketones, Leukocyte esterase, Microscopic Examination, Nitrites, pH, Protein

- **URINE DRUG SCREENING:**

  Alcohol test, Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Cotinine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

- **LIPID PANEL**

  Low Density Lipoprotein (LDL) - Cholesterol, High Density Lipoprotein (HDL) - Cholesterol, Triglycerides

- **THYROID PANEL:**

  Free T3, Free T4, Thyroid stimulating hormone (TSH)

- **SEROLOGY PANEL**:

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

  Note: The lab will report results for HIV Ab, which detects both HIV-1 Ab and HIV-2 Ab.

- **COAGULATION PANEL:**

  International Normalized Ratio (INR), activated Partial Thromboplastin time (aPTT), Prothrombin time (PT).

- **OTHER TESTS:**

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

Laboratory reports will be initialled 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.

APPENDIX 4. POTENTIALLY CLINICALLY SIGNIFICANT (PCS) LABORATORY CRITERIA

Category Parameter Name Age/Gender Restriction, if any	PCS Range (SI units) – Low	PCS Range (SI units) – High
HEMATOLOGY		
WBC	≤ 2.8 x 10^9/L	≥ 16 x 10^9/L
Neutrophils (abs)	< 0.5 x 10^9/L	> 13.5 x 10^9/L
Lymphocytes (abs)	N/A	> 12 x 10^9/L
Monocytes (abs)	N/A	> 2.5 x 10^9/L
Eosinophils (abs)	N/A	> 1.6 x 10^9/L
Basophils (abs)	N/A	> 1.6 x 10^9/L
Neutrophils (relative)	≤ 0.15	> 0.85
Lymphocytes (relative)	N/A	≥ 0.75
Monocytes (relative)	N/A	≥ 0.15
Eosinophils (relative)	N/A	≥ 0.10
Basophils (relative)	N/A	≥ 0.10
Hemoglobin		
Male	≤ 115 g/L	≥ 190 g/L
Female	≤ 95 g/L	≥ 175 g/L
Hematocrit		
Male	≤ 0.37	≥ 0.60
Female	≤ 0.32	≥ 0.54
RBC	≤ 3.5 x 10^{12}/L	≥ 6.4 x 10^{12}/L
Platelet Count	≤ 75 x 10^9/L	≥ 700 x 10^9/L
SERUM CHEMISTRY		
Sodium	< 130 mmol/L	> 150 mmol/L
Potassium	< 3 mmol/L	> 5.5 mmol/L
Chloride	≤ 90 mmol/L	≥ 118 mmol/L
Calcium	< 1.75 mmol/L	≥ 3.1 mmol/L
Phosphate	< 0.65 mmol/L	> 1.65 mmol/L
Bicarbonate	< 15.1 mmol/L	> 34.9 mmol/L
Magnesium	< 0.4 mmol/L	> 1.23 mmol/L
AST	N/A	≥ 3 x ULN
ALT	N/A	≥ 3 x ULN
Alkaline Phosphatase	N/A	≥ 1.5 x ULN
CK	N/A	> 2.5 x ULN
Creatinine	N/A	≥ 177 umol/L
BUN	N/A	≥ 10.7 mmol/L
Total bilirubin	N/A	≥ 34.2 umol/L OR > 2 x ULN
Total protein	≤ 45 g/L	≥ 100 g/L
Albumin	≤ 25 g/L	N/A

Category Parameter Name Age/Gender Restriction, if any	PCS Range (SI units) – Low	PCS Range (SI units) – High
HDL-Cholesterol	< 0.78 mmol/L	N/A
LDL-Cholesterol	N/A	> 4.9 mmol/L
Triglycerides	N/A	> 3.42 mmol/L
Uric acid		
Male	N/A	> 595 umol/L
Female	N/A	> 476 umol/L
Glucose	< 2.78 mmol/L	> 13.9 mmol/L
HbA1c	N/A	≥ 0.075
Prolactin	N/A	≥ 5 x ULN
URINALYSIS		
RBC	N/A	> 25 hpf
WBC	N/A	> 25 hpf
COAGULATION		
aPTT	N/A	> 1.5 x ULN
INR	N/A	> 1.5 x ULN
PT	N/A	> 1.5 x ULN

APPENDIX 5. PRECISION PRESENTATION OF STATISTICAL RESULTS

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Q1, Q3, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N
    - Mean, median, and 95% CI: N + 1
    - SD: N + 2
    - 25^{th} percentile (Q1): N+1
    - 75^{th} percentile (Q3): N+1
- For CGI-S score, 2 decimal places will be presented for mean, median, Q1, Q3 and 95% CI; 3 decimal places will be presented for SD; 0 decimal places will be presented for minimum and maximum. 0 decimal places will be presented in listings.
- For the calculated UPSM scores: No rounding will be applied in the ADaM datasets. 3 decimal places will be presented for mean, median, Q1, Q3; 4 decimal places will be presented for SD; 2 decimal places will be presented for min and max. 2 decimal places will be presented in listings.
- For the calculated parameter of BMI: No rounding will be applied in the ADaM datasets. 2 decimal places will be presented for mean, median, Q1, Q3; 3 decimal places will be presented for SD; 1 decimal places will be presented for min and max. 1 decimal place will be presented in listings.
- For the calculated parameter of SAS mean score: No rounding will be applied in ADaM datasets. 2 decimal places will be presented for mean, median, Q1, Q3; 3 decimal places will be presented for SD; 1 decimal places will be presented for min and max. 1 decimal place will be presented in listings.
- For lab data only: in the rare case where raw data has more than 3 decimal places, summary statistics will be presented for the scenario of N = 3. All decimals will be presented in listings.
- For plasma concentration data: No rounding will be applied in the ADaM datasets. Summary statistics (arithmetic mean, SD, 95% CI for the mean, CV%, geometric mean, geometric CV%, median, min, max) will be presented to 3 significant figures. All decimals will be presented in listings.

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  - 77 (100.0%)
  - 50 (64.9%)
  - 0 (0.0%)
- • Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule. E.g.,
  - (<0.1%)
  - (6.8%)
  - (>99.9%)
- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, no percentages should appear in the output.

Confidence Intervals:

- As a rule confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:
  - (-0.12, -0.10)
  - (9.54, 12.91)

P-values:

- P-values should be reported to 4 decimal places. P-values less than 0.0001 will be displayed as <0.0001 in the tables, and P-values greater than 0.9999 will be displayed as >0.9999.

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in an end-of-text table or subject listing.

APPENDIX 6. ADVERSE EVENTS OF POTENTIAL DRUG ABUSE AND DEPENDENCE

To ensure comprehensive and consistent selection of terminology used for analyses of drug abuse and dependence in ongoing / planned studies of SEP-363856, MedDRA PTs were identified from the following sources:

- FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (CDER, 2017; noted that the Guidance reflects MedDRA version 20.0 terminology)
- MedDRA version 22.0 SMQ: Drug abuse and dependence [20000101], Broad
- FDA FMQ: Study Agent Abuse Potential, Broad (released at FDA public workshop "Advancing Premarket Safety Analytics", held September 14, 2022)

Description:

Preferred terms were tabulated using MedDRA version 22.0 from the sources listed above. All PTs within the FDA Abuse Potential Guidance were included. All PTs listed in the MedDRA version 22.0 SMQ for Drug abuse and dependence [20000101] were included. For the FDA Study Agent Abuse Potential FMQ: No associated MedDRA PT was found for the term "Hypnogogic hallucination", and this is therefore not included. SMPA evaluates 'Drug withdrawal' as a unique medical concept using MedDRA version 22.0 SMQ for Drug withdrawal [20000102] (Broad); any overlapping PTs from the Drug withdrawal SMQ which are listed in the FDA Study Agent Abuse Potential FMQ are not included. All other PTs listed in the FDA FMQ were included.

The table below depicts the preferred terms by source.

FDA Guidance 2017		SMQ 20000101		FDA FMQ	
PT	**Code**	**PT**	**Code**	**PT**	**Code**
-	-	Accidental overdose	10000381	Accidental overdose	10000381
-	-	-	-	Acute psychosis	10001022
Aggression	10001488	-	-	-	-
Behavioural addiction	10081939	-	-	-	-
Confusional state	10010305	-	-	-	-
-	-	-	-	Delusion of grandeur	10012241
-	-	-	-	Delusional perception	10012258
Dependence	10012335	Dependence	10012335	Dependence	10012335
-	-	-	-	Depersonalisation	10012357
-	-	-	-	Derealisation disorder	10077810
-	-	-	-	Detoxification	10061814
-	-	-	-	Disinhibition	10013142
Disorientation	10013395	-	-	-	-
-	-	Disturbance in social behaviour	10061108	-	-
Dizziness	10013573	-	-	-	-
Dopamine dysregulation syndrome	10067468	Dopamine dysregulation syndrome	10067468	-	-
-	-	Drug abuse	10013654	Drug abuse	10013654
-	-	Drug abuser	10061111	Drug abuser	10061111

FDA Guidance 2017		SMQ 20000101		FDA FMQ	
PT	**Code**	**PT**	**Code**	**PT**	**Code**
-	-	Drug dependence	10013663	Drug dependence	10013663
Drug dependence, antepartum	10013675	Drug dependence, antepartum	10013675	Drug dependence, antepartum	10013675
Drug dependence, postpartum	10013676	Drug dependence, postpartum	10013676	Drug dependence, postpartum	10013676
-	-	Drug detoxification	10052237	Drug detoxification	10052237
-	-	Drug diversion	10066053	Drug diversion	10066053
-	-	Drug level above therapeutic	10061132	-	-
-	-	Drug level increased	10013722	-	-
-	-	Drug screen	10050837	-	-
-	-	Drug screen positive	10049177	-	-
Drug tolerance	10052804	Drug tolerance	10052804	-	-
Drug tolerance decreased	10052805	Drug tolerance decreased	10052805	-	-
Drug tolerance increased	10052806	Drug tolerance increased	10052806	-	-
Drug use disorder	10079381	Drug use disorder	10079381	Drug use disorder	10079381
-	-	Drug use disorder, antepartum	10079382	Drug use disorder, antepartum	10079382
-	-	Drug use disorder, postpartum	10079383	Drug use disorder, postpartum	10079383
-	-	-	-	Energy increased	
Euphoric mood	10015535	-	-	Euphoric mood	10015535
Feeling abnormal	10016322	-	-	-	-
Feeling drunk	10016330	-	-	Feeling drunk	10016330
-	-	-	-	Feeling jittery	10016338
Feeling of relaxation	10016352	-	-	Feeling of relaxation	10016352
-	-	-	-	Flight of ideas	10016777
Hallucination	10019063	-	-	Hallucination	10019063
Hallucination, auditory	10019070	-	-	Hallucination, auditory	10019070
Hallucination, gustatory	10019071	-	-	Hallucination, gustatory	10019071
Hallucination, olfactory	10019072	-	-	Hallucination, olfactory	10019072
Hallucination, synaesthetic	10062824	-	-	Hallucination, synaesthetic	10062824
Hallucination, tactile	10019074	-	-	Hallucination, tactile	10019074
Hallucination, visual	10019075	-	-	Hallucination, visual	10019075
Hallucinations, mixed	10019079	-	-	Hallucinations, mixed	10019079
Inappropriate affect	10021588	-	-	Hallucination, gustatory	10019071
-	-	-	-	Hypersomnia	10020765
-	-	-	-	Hypervigilance	10048533

FDA Guidance 2017		SMQ 20000101		FDA FMQ	
PT	**Code**	**PT**	**Code**	**PT**	**Code**
-	-	-	-	Hypnagogic hallucination	10020927
-	-	-	-	Hypnogogic hallucination	No such code
-	-	-	-	Hypnopompic hallucination	10020928
-	-	-	-	Inappropriate affect	10021588
-	-	-	-	Infant sedation	10082187
-	-	-	-	Intentional misuse of drug delivery system	10081675
-	-	Intentional overdose	10022523	Intentional overdose	10022523
-	-	Intentional product misuse	10074903	Intentional product misuse	10074903
-	-	Intentional product use issue	10076308	-	-
-	-	-	-	Mania	10026749
-	-	Maternal use of illicit drugs	10026938	-	-
-	-	Medication overuse headache	10072720	-	-
-	-	-	-	Mixed delusion	10076429
Mood altered	10027940	-	-	Mood altered	10027940
Mood swings	10027951	-	-	-	-
-	-	Narcotic bowel syndrome	10072286	-	-
-	-	Needle track marks	10028896	-	-
-	-	Neonatal complications of substance abuse	10061862	-	-
-	-	-	-	Neonatal oversedation	10050395
-	-	Overdose	10033295	-	-
-	-	-	-	Paranoia	10033864
-	-	-	-	Post-injection delirium sedation syndrome	10072851
-	-	Prescription drug used without a prescription	10076639	-	-
-	-	Prescription form tampering	10067669	Prescription form tampering	10067669
-	-	-	-	Psychomotor hyperactivity	10037211
Psychotic disorder	10061920	-	-	-	-
		Reversal of opiate activity	10039004	-	-

FDA Guidance 2017		SMQ 20000101		FDA FMQ	
PT	**Code**	**PT**	**Code**	**PT**	**Code**
-	-	-	-	Sedation	10039897
-	-	-	-	Sedation complication	10079741
Somnolence	10041349	-	-	Somnolence	10041349
-	-	-	-	Somnolence neonatal	10041350
-	-	-	-	Stupor	10042264
-	-	Substance abuse	10066169	Substance abuse	10066169
-	-	Substance abuser	10067688	Substance abuser	10067688
-	-	Substance dependence	10076595	Substance dependence	10076595
-	-	Substance use	10070964	-	-
Substance use disorder	10079384	Substance use disorder	10079384	Substance use disorder	10079384
-	-	Substance-induced mood disorder	10072387	Substance-induced mood disorder	10072387
-	-	Substance-induced psychotic disorder	10072388	Substance-induced psychotic disorder	10072388
-	-	-	-	Suspected product tampering	10079404
Thinking abnormal	10043431	-	-	-	-
-	-	Toxicity to various agents	10070863	-	-
-	-	-	-	Transient psychosis	10056326
-	-	-	-	Withdrawal hypertension	10048007

APPENDIX 7. INTERNATIONALLY AGREED ORDER FOR SYSTEM ORGAN CLASS

Internationally Agreed Order
Infections and infestations
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Blood and lymphatic system disorders
Immune system disorders
Endocrine disorders
Metabolism and nutrition disorders
Psychiatric disorders
Nervous system disorders
Eye disorders
Ear and labyrinth disorders
Cardiac disorders
Vascular disorders
Respiratory, thoracic and mediastinal disorders
Gastrointestinal disorders
Hepatobiliary disorders
Skin and subcutaneous tissue disorders
Musculoskeletal and connective tissue disorders
Renal and urinary disorders
Pregnancy, puerperium and perinatal conditions
Reproductive system and breast disorders
Congenital, familial and genetic disorders
General disorders and administration site conditions
Investigations
Injury, poisoning and procedural complications
Surgical and medical procedures
Social circumstances
Product issues