STATISTICAL ANALYSIS PLAN

SEP380-303

A 12-MONTH OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFECTIVENESS OF SEP-4199 CONTROLLED RELEASE (CR) FOR THE TREATMENT OF MAJOR DEPRESSIVE EPISODE ASSOCIATED WITH BIPOLAR I DISORDER (BIPOLAR I DEPRESSION)

PHASE: PHASE III

[redacted]

VERSION NUMBER AND DATE: FINAL, 25JAN2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final (Dated 25JAN2024) for Protocol SEP380-303.

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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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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	17NOV2023	[redacted]	Not Applicable – First Version
2.0	01DEC2023	[redacted]	Incorporated comments on the first draft.
2.1	18DEC2023	[redacted]	Incorporated comments on the final draft.
Final	25JAN2024	[redacted]	Finalization.

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2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol SEP380-303. 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 protocol version 2.0, dated 07SEP2021.

The Data and Safety Monitoring Board (DSMB) analysis plan will be described in a separate document. An Important Protocol Deviation (IPD) Review Plan and a Pre-lock Data Review (PLDR) Plan will be written to describe the process and the outputs to be delivered during the IPD/PLDR meetings.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. STUDY OBJECTIVES

The objective of Study SEP380-303 is to evaluate the long-term safety, tolerability, and effectiveness of SEP-4199 CR at a flexible daily dose of 200 mg/day or 400 mg/day in subjects who previously completed the 6 weeks lead-in Study SEP380-301 of SEP-4199 CR for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression).

3.1.1. PRIMARY OBJECTIVE

The primary objective of the current study is to evaluate the long-term safety and tolerability of treatment with SEP-4199 CR 200-400 mg/day, as reflected in rates of adverse events (AEs), discontinuations due to an AE, serious AEs (SAEs), and adverse events of special interest (AESI).

3.1.2. OTHER SAFETY OBJECTIVES

Long-term safety and tolerability of flexible-dose SEP-4199 CR treatment will be evaluated as follows:

- Measurements including 12-lead electrocardiogram (ECG), clinical laboratory values, vital signs, body weight, and metabolic parameters
- Prolactin levels
- Manic symptoms using the Young Mania Rating Scale (YMRS)
- Suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Movement disorders using the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and modified Simpson-Angus Scale (SAS)
- Potential for withdrawal symptoms after discontinuation, using the Physician's Withdrawal Checklist (PWC).

3.1.3. EFFECTIVENESS OBJECTIVES

Long-term effectiveness of flexible-dose SEP-4199 CR treatment will be evaluated as follows:

- Severity of depression symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS)
- Overall bipolar depression severity assessed using the Clinical Global Impression-Bipolar Version-Severity of Illness (CGI-BP-S) Depression scale

• Anxiety symptoms severity assessed using the clinician-administered Hamilton Anxiety Rating Scale (HAM-A)

• Severity of subject-reported depression symptoms as measured by the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16)

• Functional impairment, as measured by the Sheehan Disability Scale (SDS)

• Quality of life, as measured by the EuroQol - 5 Dimension - 5 Level (EQ-5D-5L)

• Anhedonia symptoms, as measured by the Snaith-Hamilton Pleasure Scale (SHAPS).

3.1.4. PHARMACOKINETIC/PHARMACODYNAMIC OBJECTIVES

• Perform population pharmacokinetic (Pop-PK) analysis using plasma SEP-4199 concentrations.

• Explore the relationship between MADRS score and plasma SEP-4199 exposure using population PK/pharmacodynamics (PD) methods.

• Explore the relationship between safety outcomes and plasma SEP-4199 exposure.

3.2. STUDY ENDPOINTS

3.2.1. PRIMARY ENDPOINTS

• The incidence of overall AEs, discontinuation due to AEs, and SAEs

3.2.2. OTHER SAFETY ENDPOINTS

• The incidence of AESI including but not limited to hyperprolactinemia-related AEs

• Clinical laboratory evaluations (serum chemistry, hematology, thyroid panel, urinalysis)

• Clinical evaluation (vital signs including orthostatic effects, and 12-lead ECG measurements)

• Changes in prolactin values

• Changes in metabolic parameters (insulin, glucose, hemoglobin A1c (HbA1c), lipid panel)

• Change and percent change in body weight

• Change in body mass index (BMI)

• Incidence of treatment-emergent mania, defined as a YMRS total score ≥ 16 at post-Baseline visit (scheduled or unscheduled), or an adverse event of hypomania or mania

• Changes from Baseline in movement disorders scales: AIMS, BARS, and modified SAS

• Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS

• Change from Week 52/EOT (end of treatment) visit to the safety follow-up visit on the PWC

3.2.3. EFFECTIVENESS ENDPOINTS

• Changes in MADRS total score

• Changes in CGI-BP-S depression score

• The proportion of subjects with treatment response, defined as ≥ 50% reduction from Baseline in MADRS total score

• The proportion of subjects meeting criteria for remission, defined as MADRS total score ≤ 12

• Changes in HAM-A total score

- Changes in QIDS-SR16 total score
- Changes in SDS total and subscale scores (work/school, family, and social function)
- The proportion of subjects meeting criteria for functional remission, defined as having a score ≤ 2 on each of the SDS subscale scores (work/school, family, and social function)
- Changes in the EQ-5D-5L Visual Analog Scale (VAS) and Index scores
- Changes in the SHAPS total score

3.2.4. PHARMACOKINETIC AND PHARMACODYNAMIC ENDPOINTS

- Plasma concentrations of aramisulpride and esamisulpride
- Plasma concentrations of prolactin

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

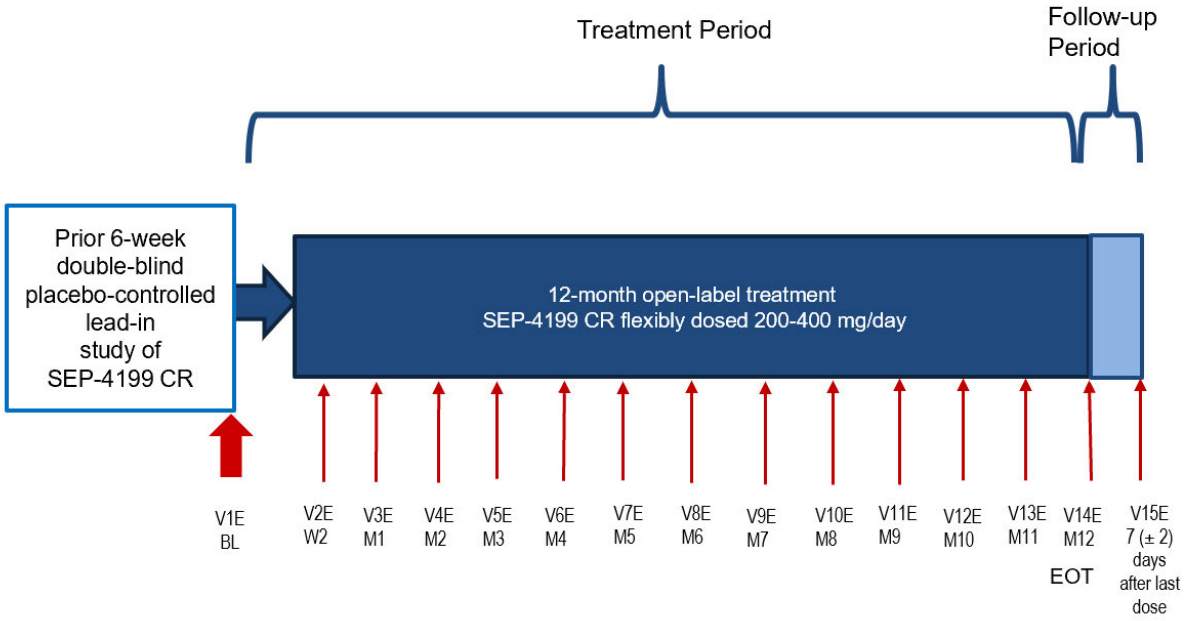
SEP380-303 is a 12-month open-label safety extension study to evaluate the long-term safety, tolerability, and effectiveness of SEP-4199 CR 200-400 mg/day in the treatment of subjects with bipolar I depression who previously completed a lead-in study of SEP-4199 CR.

The study will consist of a 12-month open-label flexible-dose treatment period, and a safety follow-up period, as shown in the following figure. There are 15 scheduled visits, including a Baseline visit, 13 visits during the open-label treatment period, and 1 safety follow-up visit 7 (± 2) days after the last dose of study drug. If necessary, subjects may return to the clinic at any time for an unscheduled visit (see Figure 1).

Subjects who meet the entry criteria will transition immediately at the End of Treatment (EOT) visit from Study SEP380-301. The EOT visit from studies SEP380-301 will generally serve as the Baseline visit for the present study. Informed consent will be obtained from all subjects before any study procedures are performed for the present study.

A study schematic is presented in Figure 1.

Figure 1: Study schematic – All Subjects



Note: All subjects are to take SEP-4199 CR 200 mg beginning on Day 1, the day following Baseline (Visit 1E). There is an extra visit for Japan (Visit1EJ) on Day 1 (evaluates ECG).
Abbreviations: BL = Baseline; CR = controlled release; EOT = end of treatment. V = visit; E = extension; W = Week; M = Month

4.2. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

There is an open-label study and no randomization planned in this study. All subjects will receive flexible dosing with SEP-4199 CR 200 mg/day or 400 mg/day during the 52 weeks of treatment.

4.3. BLINDING

This is an open-label study. All subjects will receive flexible dosing with SEP-4199 CR 200 mg/day or 400 mg/day.

4.4. DETERMINATION OF SAMPLE SIZE

All subjects who complete the 6-week double-blind treatment period in Study SEP380-301 are eligible to enrol in the current study. Assuming a completion rate of 85% in the SEP-4199 CR Study SEP380-301 and 80% rollover rate of completers from that study to the current extension study, it is estimated that approximately 355 subjects will be enrolled in this study. Due to early termination of the Study SEP380-301, there are 64 subjects were enrolled in this study.

4.5. CHANGES IN THE CONDUCT OF THE STUDY

The first subject was enrolled on ddmmm2022 under protocol Version 1.00 (dated 20MAY2021). Additional protocol versions and amendments are listed below.

- Protocol version 2.00 (7SEP2021); Amendment 1.00 (7SEP2021).

4.6. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1, Table 2 of the Clinical Study Protocol (CSP). This table is also included in APPENDIX 7 of the SAP.

4.7. CHANGES TO ANALYSIS FROM PROTOCOL

Because of the small sample size due to study early termination, the following main changes will be made for this study:

1. Only 2 treatment groups will be formed based on a subject's previous participation in the lead-in study of SEP-4199 CR (SEP-SEP: previously randomized to any SEP-4199 CR dose group and PBO-SEP: previously randomized to placebo).
2. No subgroup summaries will be performed.
3. No summaries using Follow-up population will be performed.
4. Except for PWC, follow-up period summaries will not be performed, PWC will be summarized by Safety population.
5. AE will not be summarized by high-level term (HLT).
6. No Kaplan-Meier curves will be plotted for time to discontinuation and time to the earliest onsets of the selected AESI. The Kaplan-Meier estimation will also not be performed.
7. To be consistent with AIMS and BARS, MSAS will be summarized by total score.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for independent DSMB meetings
- Final Analysis

5.1. DATA AND SAFETY MONITORING BOARD

A DSMB SAP and charter, describing the methodology, meeting schedule, and presentation of results as well as access to results will be maintained by another Contract Research Organization (CRO) and SMPA as separate documents. All DSMB analyses will be performed independently by the CRO approximately three times a year.

5.2. INTERIM ANALYSIS

There is no interim analysis of efficacy data planned for this study.

5.3. FINAL ANALYSIS

All final, planned analyses specified in this SAP will be performed inhouse by SMPA following this SAP, after database lock.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6. ANALYSIS POPULATIONS

Agreement and authorization of enrolled subjects included/excluded from the analysis population listed below will be conducted prior to database lock.

Enrolled subjects in SEP380-303 will include all subjects who signed the informed consent form (ICF) of study 380-303.

6.1. SAFETY POPULATION

The Safety Population will consist of all subjects who are enrolled and have received at least one dose of study drug during the 52-week open-label extension treatment period. The Safety Population will be used for the long-term safety, tolerability, and efficacy analyses. Subjects will be analyzed according to the following 3 treatment groups:

- PBO-SEP: Subjects whose actual treatment group is Placebo in study SEP380-301 and received SEP-4199 CR in study SEP380-303.
- SEP-SEP: Subjects whose actual treatment group is either SEP-4199 CR 200 mg/day or SEP-4199 CR 400 mg/day in study SEP380-301 and received SEP-4199 CR in study SEP380-303.
- ALL EXT: all subjects received SEP-4199 CR in study SEP380-303.

7. GENERAL 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 OLE study medication of study SEP380-303 (Day 1 is the Study Day of the first dose of OLE study medication of study SEP380-303).

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

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

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

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

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, double-blind (DB) Baseline is defined as the last non-missing measurement taken prior to the first dose of study medication of study SEP380-301, including unscheduled assessments. DB Baseline values are essentially the "Baseline" values of study SEP380-301 and will be directly obtained from the SEP380-301 ADaM datasets.

Open-label (OL) Baseline is defined as the last non-missing measurement taken prior to the first dose of OLE study medication of study SEP380-303, including unscheduled assessments. These values will be derived in SEP380-303 ADaM datasets using data collected in studies SEP380-301 and SEP380-303.

Whenever available, the time information should be accounted for in the derivation of OL 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 OLE study medication coincide, that measurement will be considered the OL Baseline.

7.3. DERIVED TIMEPOINTS

The last non-missing post-OL Baseline (i.e., post first OLE dose) measurement collected up to and including the Visit 14E (EOT/ET) measurement and within 7 days post the last OLE dose will be carried forward and defined as the last observation carried forward (LOCF) endpoint. Both scheduled and unscheduled assessments as well as the early termination assessments that are collected during this period will contribute to the derivation of the LOCF endpoint. However, scheduled and unscheduled measurements taken after the Visit 14E (EOT/ET) measurement or beyond 7 days post the last OLE dose will not be used in the derivation.

The study visits will be mapped to analysis visits for table summaries (Table 1).

Table 1: Mapping of study visits to analysis visits.

Study Visit	Analysis Visit Number	Analysis Visit
NA*	0	DB Baseline
Visit 1E	1	OL Baseline
Visit 1EJ#	1.1	OL Day 1
Visit 2E	2	OL Week 2
Visit 3E	3	OL Month 1
Visit 4E	4	OL Month 2
Visit 5E	5	OL Month 3
Visit 6E	6	OL Month 4
Visit 7E	7	OL Month 5
Visit 8E	8	OL Month 6
Visit 9E	9	OL Month 7

Visit 10E	10	OL Month 8
Visit 11E	11	OL Month 9
Visit 12E	12	OL Month 10
Visit 13E	13	OL Month 11
Visit 14E (if representing true EOT visit). For ET visit mapping see Section 7.4	14	OL Month 12
Visit 15E	15	Follow-up

* Several assessments from that visit are collected in SEP380-301 study. #An extra visit for Japan (Visit 1EJ) on Day 1 that evaluates ECG.

Original study visit collected on the case report forms (CRFs) will be displayed in the listings.

7.4. RETESTS, UNSCHEDULED VISITS, AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the planned visits where assessment is intended to be given and collected within 7 days post the last OLE dose will be presented, as well as the derived DB and OL Baseline values and the LOCF value.

Unscheduled measurements will not be included in by-visit summaries as a separate time point. However:

- Unscheduled measurements collected prior to the first dose of study medication in SEP380-301 contributed to the derivation of the DB Baseline value.
- Unscheduled measurements collected in SEP380-301 or SEP380-303 prior to the first dose of OLE study medication in SEP380-303 will contribute to the derivation of the OL Baseline value.
- Unscheduled measurements collected post-OL Baseline up to and including 7 days post the last OLE dose in SEP380-303 will contribute to the derivation of the LOCF value, the potential clinically significant (PCS) value, and the best/worst case value where required (e.g., shift table).

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.

As per protocol, study Visit 14E can be a Week 52/End of Treatment (EOT) visit or an Early Termination (ET) visit. If a subject terminates early, his/her measurements taken at the ET visit and within 7 days post the last OLE dose will be mapped to the next planned visit (after the last scheduled visit the subject attended) during which that assessment was expected to be performed as specified by the Schedule of Assessments table in the protocol. This applies to both efficacy and safety data. ET measurements taken beyond 7 days post the last OLE dose will not be mapped.

Listings will include scheduled, unscheduled, retest, and early discontinuation data without regard to the 7-day window, with original dates and visits displayed.

7.5. WINDOWING CONVENTIONS

No visit windowing will be performed during the analysis for this study. Data will be analyzed according

to the schedule outlined in the CSP. However, with the exception of SAE and PWC, any data collected beyond 7 days post the last OLE dose will be excluded from the efficacy and safety analyses unless otherwise specified; these data will be presented in data listings only.

7.6. STATISTICAL TESTS

No statistical inference will be made for this open-label extension study.

7.7. COMMON CALCULATIONS

Below derivation will be applied separately for both DB Baseline and OL Baseline as appropriate.

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

- Assessment Value at Visit X - Baseline Value

For quantitative measurements, percentage change from Baseline will be calculated as:

- (Test Value at Visit X - Baseline Value) × 100 / Baseline Value

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No statistical comparison will be conducted, so no adjustments for covariates and factors are to be considered.

8.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in the US and non-US countries, including Bulgaria, Romania, and Japan.

Center pooling will not be implemented in the analyses for this open-label extension study.

8.3. MISSING DATA

Individual missing items in any rating scale will not be imputed in any analysis. When calculating a total score, subscale score, or any summary scores based on more than one item, if one or more items are missing at a visit, then the associated summary score will be set to missing. For additional details, see the individual scale description sections.

- Handling of missing efficacy data, if any, is described in Section 17.2.
- Handling of missing safety data, if any, is described in Sections 18.1.1 and 18.6.
- See APPENDIX 2 for details of handling incomplete/missing dates.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No statistical comparison will be conducted, so no multiplicity adjustment will be performed.

8.5. EXAMINATION OF SUBGROUPS

Because the small sample size, no subgroup analysis will be conducted for this study.

9. 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 separately.

10. DISPOSITION AND WITHDRAWALS

Unless otherwise specified, the disposition summary tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

All subjects who were enrolled in study SEP380-303 will be accounted for in this study.

Subject disposition will be presented by the actual treatment group. The number and percentage of subjects who enrolled in study SEP380-303, received at least one dose of OLE study medication, enrolled but did not receive OLE study medication, and completed or discontinued from the OLE treatment period (including reasons for discontinuation) will be presented.

Discontinuation by visit will be summarized for the enrolled subjects by the actual treatment group.

The number and percentage of enrolled subjects will also be summarized by region, country, and site, by the actual treatment group.

11. IMPORTANT PROTOCOL DEVIATIONS

Important protocol deviations (IPDs) will be identified and documented for all subjects based on reviews of data listings and the protocol deviations log; the data will be presented separately.

Unless otherwise specified, the IPD summary tables will include the following columns: PBO-SEP, SEP-SEP (S200-SEP and S400-SEP combined), and ALL EXT (all rollovers from SEP380-301).

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

- Did not satisfy inclusion and/or exclusion criteria for study SEP380-303.
- Received prohibited medication in study SEP380-303.

IPDs will be identified for all subjects enrolled in study SEP380-303 and presented in a data listing. The number and percentage of subjects within each IPD category will be summarized by the actual treatment for the Safety Population.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, the demographic and Baseline characteristics summary table will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

Demographic data and other Baseline characteristics will be presented for the Safety Population by the actual treatment group.

The following demographic and other Baseline characteristics will be reported for this study. According to protocol, year of birth, age, and sex collected in the core studies are re-entered into the eCRF of SEP380-303. For statistical analysis, date of birth, age, sex, race, and ethnicity will be retrieved from the ADaM datasets of studies SEP380-301. Unless otherwise specified, the categories below apply to all subjects:

- Age (years) - calculated relative to date of informed consent in SEP380-301, as a continuous variable
- Age (years) categories:
  - < 55 years
  - ≥ 55
- Sex:
  - Female
  - Male
- Race:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other
- Ethnicity:
  - Hispanic or Latino
  - Not Hispanic or Latino
- Country:
  - United States
  - Bulgaria
  - Japan
  - Romania
- Geographic region:
  - USA
  - Europe
  - Japan

- DB Baseline Height (cm), as a continuous variable
- DB Baseline and OL Baseline Weight (kg), as a continuous variable
- DB Baseline and OL Baseline BMI (kg/m²), as a continuous variable
- DB Baseline and OL Baseline BMI (kg/m²) category:
  - Underweight: <18.5 kg/m²
  - Normal: ≥18.5 to <25.0 kg/m²
  - Overweight: ≥25.0 to <30.0 kg/m²
  - Obese: ≥30.0 kg/m²
- DB Baseline and OL Baseline MADRS Total Score, as a continuous variable
- DB Baseline and OL Baseline CGI-BP-S Score, as a continuous variable

The following psychiatric history data will be summarized for Safety Population by the actual treatment in a separate table. All values were collected or derived in the SEP380-301 study:

- Time since initial onset of bipolar I disorder (years) - calculated relative to date of informed consent in SEP380-301
- Age at initial onset of bipolar I disorder (years)
- Time since onset of current episode of major depression associated with bipolar I disorder symptoms (months) - calculated relative to date of informed consent in SEP380-301
- Bipolar I diagnosis subtype:
  - Bipolar I disorder without rapid cycling
  - Bipolar I disorder with rapid cycling
- Number of prior hospitalizations for treatment of bipolar I disorder:
  - 0
  - 1
  - 2
  - 3
  - 4 or more
- Any other current psychiatric disorders:
  - Yes
  - No

Diagnosis and DSM-5 code for any other current psychiatric disorders will be summarized in a separate table for Safety Population. These other current psychiatric disorders will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0, and presented by System Organ Class (SOC) and Preferred Term (PT).

12.1. DERIVATIONS

- BMI expressed in kg/m^2:

Weight (kg)/ [height (cm)/100]^2

All other derivations are detailed in SEP380-301 Statistical Analysis Plan, and all derivations are done in SEP380-301 ADaM datasets.

13. MEDICAL HISTORY

Unless otherwise specified, the medical and surgical history summary tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

Medical and surgical history information, including both past and concomitant medical conditions and major surgical history, as collected on the "*Medical History*" CRF form of study SEP380-301, will be coded using MedDRA, Version 22.0, and presented by SOC and PT for the Safety Population by the actual treatment. Data will be sorted by SOC based on the internationally agreed order (see APPENDIX 4) and by PT in decreasing frequency in the "ALL EXT" column.

14. PRIOR AND CONCOMITANT MEDICATIONS

Unless otherwise specified, the concomitant medications summary tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

Medications will be coded to Anatomical Therapeutic Chemical (ATC) Levels and Preferred Names according to World Health Organization Drug (WHODRUG) dictionary, Version SEP2021.

Whenever available, the time information should be accounted for in the derivation of prior, concomitant, and post-treatment medications. See APPENDIX 2 for the handling of partial dates for medications.

- Prior medications are medications which started prior to the first dose of OLE study medication.
- Concomitant medications are medications which started at the same time of or after the first dose of OLE study medication and at the same time of or before the last dose of OLE study medication; or started prior to and ended at the same time of or after the first dose of OLE study medication; or started at the same time of or prior to the last dose of OLE study medication and marked as ongoing.
- Post-treatment medications are medications which stopped after the last dose of OLE study medication or ongoing.

Concomitant medication use will be summarized by ATC Level 3 and Preferred Name for the Safety Population by the actual treatment. If ATC Level 3 is missing, then ATC Level 2 will be used. Medications will be sorted by ATC Level 3 alphabetically and by Preferred Name in decreasing frequency in the "ALL EXT" column.

Prior, concomitant, and post-treatment medications will be provided in data listings.

15. STUDY MEDICATION EXPOSURE

Unless otherwise specified, the study medication exposure summary tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

Exposure to OLE study medication data will be summarized for the Safety Population by the actual treatment group.

The date/time of first dose of OLE study drug and the date/time of last dose of OLE study drug will be respectively derived as the earliest ("Date Dosing Started" & "Time Dosing Started") pair and the latest ("Date Dosing Ended" & "Time Dosing Ended") pair as collected on the "*Study Drug Administration / Drug Accountability*" CRF form. The start and end dates/times from blister cards with the number of tablets dispensed equal to the (number of tablets returned + number of tablets reported lost) are excluded from the derivation.

Duration of exposure (in days) will be summarized both as a continuous variable for the OLE treatment period and categorically:

- Number and percentage of subjects with OLE study drug exposure ≥ 1, ≥ 14, ≥ 30, ≥ 60, ≥ 90, ≥ 120, ≥ 150, ≥ 180, ≥ 210, ≥ 240, ≥ 270, ≥ 300, ≥ 330, and ≥ 360 days;

- Number and percentage of subjects with OLE study drug exposure for 1 - 13, 14 - 29, 30 - 59, 60 - 89, 90 - 119, 120 - 149, 150 - 179, 180 – 209, 210 – 239, 240 – 269, 270 -299, 300 – 329, 330 – 359, and ≥ 360 days.

Total person-years of exposure to OLE study medication will be calculated for each actual treatment sequence and overall for all subjects in the Safety Population.

Mean daily dose and modal daily dose will be calculated for the entire OLE treatment period and summarized.

The number of days that a subject received the CR 200 mg/day dose level, and the CR 400 mg/day dose level during the OLE treatment period will be summarized for the Safety Population both as a continuous variable and categorically:

- Number and percentage of subjects with exposure to a particular dose level for 1 - 13, 14 - 29, 30 - 59, 60 - 89, 90 - 119, 120 - 149, 150 - 179, 180 - 209, 210 – 239, 240 – 269, 270 - 299, 300 – 329, 330 – 359, and ≥ 360 days.

Duration of exposure since SEP380-301 first dose (in days) will be summarized as a continuous variable for the Safety Population by the actual treatment group.

15.1. DERIVATIONS

Per protocol, Study drug will be provided in one-week blister cards (7 days + 2 extra days) containing 9 or 18 tablets of SEP-4199 CR 200 mg tablets. The 200 mg blister cards will contain 9 tablets; subjects will be instructed to take a column of one tablet per day, according to dosing instructions. The 400 mg blister cards will contain 18 tablets; subjects will be instructed to take a column of two tablets each day, according to dosing instructions. Each subject will be dispensed two or four 9-day (7 days + 2 extra days) blister cards per scheduled visit, depending on the timing of the next scheduled visit.

- Duration of exposure (days) = date of last dose of OLE study drug – date of first dose of OLE study drug + 1. Interruptions in exposure (i.e., missed doses) and dose changes (if any) are not considered in the calculation of overall exposure.

- Duration of exposure since SEP380-301 first dose (days) = date of last dose of OLE study drug – date of first dose of study drug in SEP380-301 + 1. This calculation is only performed for the subjects whose actual treatment group is SEP-4199 CR 200, or 400 mg/day in SEP380-301. Interruptions in exposure (i.e., missed doses) and dose changes (if any) are not considered in this calculation.

- The number of days that a subject received a specific dose level (the CR 200 mg/day or CR 400 mg/day) of study medication during the OL treatment period is calculated as the cumulative days the subject is expected to take the specific dose level during the OL treatment period.

- Total person-years of exposure is the sum of all durations of exposure in days / 365.25.

- Mean daily dose (mg/day)

$$\frac{\sum \text{Dose per tablet for Visit } j \times (\text{\# Tablets Dispensed for Visit } j - \text{\# Tablets Returned for Visit } j - \text{\# Tablets Lost for Visit } j)}{\text{Duration of Exposure}}$$

If the number of tablets dispensed, returned, and/or lost as collected on the "*Study Drug Administration / Drug Accountability*" CRF form is missing for one or more visits, the mean daily dose will be calculated based on visits with complete drug accountability data available. That is, the numerator of the formula above will only include visits with the number of tablets dispensed, returned, and lost available, and the denominator should be adjusted to exclude dosing periods covered by visits excluded from the calculation (i.e., Duration of Exposure – dosing periods [sum of (EXENDTC – EXSTDTC+1)] covered by visits with missing or incomplete accountability data). If the dose level of a visit is unknown, that visit should be excluded from the calculation as well in both the numerator and the denominator.

- Modal daily dose will be determined as the daily dose that is taken for the most time (in terms of number of days) among all doses taken. If there are ties, the latest modal dose is used for summary. A subject's modal daily dose may fall in one of the categories below:

  - CR 200 mg/day
  - CR 400 mg/day

16. STUDY MEDICATION COMPLIANCE

Unless otherwise specified, the study medication compliance tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

Compliance to OLE study medication will be presented for the Safety Population, by the actual treatment group.

Percent compliance will be calculated overall for the OLE treatment period. Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the OLE treatment period. Subjects with missing compliance will not be classified as non-compliant. Compliance will be summarized both as a continuous variable and categorically (i.e., number and percentage of subjects with compliance < 75%, 75% - 125%, > 125%, and missing).

16.1. DERIVATIONS

- Overall Compliance (%) to study medication in percentage will be calculated as follows:

$$\frac{\sum(\text{\# Tablets Dispensed for Visit } j - \text{\# Tablets Returned for Visit } j - \text{\# Tablets Lost for Visit } j)}{\text{\# Tablets should be taken per day} \times \text{Duration of Exposure}} \times 100\%$$

If the number of tablets dispensed, returned, and/or lost as collected on the "*Study Drug Administration / Drug Accountability*" CRF form is missing for one or more visits, the overall compliance will be calculated based on visits with complete drug accountability data available. That is, the numerator of the formula above will only include visits with the number of tablets dispensed, returned, and lost available, and the denominator should be adjusted to exclude dosing periods covered by visits excluded from the calculation (i.e., change "Duration of Exposure" to be Duration of Exposure – dosing periods [sum of (EXENDTC – EXSTDTC+1)] covered by visits with missing or incomplete accountability data). In addition, among all the visits included in the overall compliance calculation of a subject, the first visit must have dosing start date (EXSTDTC) available and the last visit must have dosing end date (EXENDTC) available.

17. EFFICACY OUTCOMES

Unless otherwise specified, the efficacy summary tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

All analyses of the efficacy variables will be based on the Safety Population by the actual treatment group.

17.1. DERIVATION & ANALYSIS OF EFFICACY VARIABLES

17.1.1. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN MADRS TOTAL SCORE AT EACH SCHEDULED VISIT

The MADRS (Montgomery-Asberg Depression Rating Scale) 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. Total score will be equal to the sum of the 10 items (range between 0 and 60).

MADRS is assessed at Week 2 and monthly and at these study visits: from Visit 1E (coinciding with Visit 6 of SEP380-301) to Visit 14E.

The DB Baseline and OL Baseline MADRS total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in MADRS total score will be derived as described in Section 17.1.1.

The observed values of MADRS total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in MADRS total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF. The line plots of the mean (SD) of change from DB baseline as well as change from OL baseline will be created.

17.1.2. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN CGI-BP-S SCORE AT EACH SCHEDULED VISIT

The CGI-BP-S (Clinical Global Impression-Bipolar Version-Severity) 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-BP-S depression 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).

CGI-BP-S is assessed at week 2 and monthly and at these study visits: from Visit 1E (coinciding with Visit 6 of SEP380-301), to Visit 14E.

The DB Baseline and OL Baseline CGI-BP-S depression score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in CGI-BP-S depression score will be derived as described in Section 17.1.2.

The observed values of CGI-BP-S depression score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in CGI-BP-S depression score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF. The line plots of the mean (SD) of change from DB baseline as well as change from OL baseline will be created.

17.1.3. MADRS RESPONSE AT EACH SCHEDULED VISIT

MADRS response is defined as a 50% or greater improvement (i.e., decrease) in MADRS total score from DB Baseline.

The percent change in MADRS total score from DB Baseline will be calculated by:

$$\frac{\text{MADRS total score at a visit or the LOCF endpoint - MADRS total score at DB Baseline}}{\text{MADRS total score at DB Baseline}} \times 100\%$$

For each subject, the responder indicator will be set to Y if the percent change is negative and the magnitude is equal to or greater than 50%. The indicator will be set to N if the percentage is negative but the magnitude is less than 50% or if the percentage is non-negative. The indicator will be set to missing if the percentage is missing.

MADRS response will be derived for all scheduled OLE study visits and LOCF.

The number and percentage of subjects who achieve a MADRS response will be summarized descriptively for each scheduled OLE study visit (starting from Visit 1E) and LOCF.

17.1.4. MADRS REMISSION AT EACH SCHEDULED VISIT

MADRS remission is defined as MADRS total score $\leq$ 12.

For each subject, the remitter indicator will be set to Y if the MADRS total score is less than or equal to 12. The indicator will be set to N if the MADRS total score is more than 12. The indicator will be set to missing if the MADRS total score is missing.

MADRS remission will be derived for all scheduled OLE study visits and LOCF.

The number and percentage of subjects who achieve a MADRS remission will be summarized descriptively for each scheduled OLE study visit (starting from Visit 1E) and LOCF.

17.1.5. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN HAM-A TOTAL SCORE AT EACH SCHEDULED VISIT

The Hamilton Anxiety Rating Scale (HAM-A) is a clinician-administered scale that was developed to quantify the severity of anxiety symptomatology. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point (0-4) scale, with higher scores indicating greater severity.

HAM-A total score will be equal to the sum of the 14 items and ranges between 0 and 56.

HAM-A is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The DB Baseline and OL Baseline HAM-A total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in HAM-A total score will be derived as described in Section 17.1.5.

The observed values of HAM-A total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in HAM-A total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 4E) and LOCF.

17.1.6. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN QIDS-SR16 TOTAL SCORE AT EACH SCHEDULED VISIT

The Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR16) is a 16-item subject-reported depression symptom severity questionnaire. Each item is rated 0 to 3. The scoring of the QIDS-SR16 converts responses to 16 separate items into the 9 DSM-IV symptom criterion domains. The 9 domains are: sad mood (Item 5), concentration (Item 10), self-criticism (Item 11), suicidal ideation (Item 12), interest (Item 13), energy/fatigue (Item 14), sleep disturbance (early/middle/late insomnia or hypersomnia) (Items 1 to 4), decrease/increase in appetite/weight (Items 6 to 9), and psychomotor agitation/retardation (Items 15 and 16). For symptom domains that consist of more than one item, the highest score among the items relevant to the given domain is taken. The total score will be equal to the sum of the 9 domains and ranges from 0-27 with higher scores indicating greater severity.

QIDS-SR16 is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The DB Baseline and OL Baseline QIDS-SR16 total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in QIDS-SR16 total score will be derived as described in Section 17.1.6.

The observed values of QIDS-SR total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in QIDS-SR total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 4E) and LOCF.

17.1.7. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN SDS TOTAL SCORE AND SUBSCALE SCORES AT EACH SCHEDULED VISIT

The Sheehan Disability Scale (SDS) is a subject-reported assessment of function. The SDS is a composite of 3 items designed to measure the extent to which 3 major sectors in a patient's life are impaired by depressive symptoms. This anchored visual analogue scale uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability across 3 domains: work, social life or leisure activities, and home life or family responsibilities. The subject will rate his or her degree of impairment in each of these domains using an 11-point scale ranging from 0-10, with higher scores indicating more impairment. There are verbal descriptors for the points on the scale as well as numerical scores that provide more precise levels of the verbal descriptors. Scores for the 3 items are summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired).

SDS is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The DB Baseline and OL Baseline SDS total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in SDS total score will be derived as described in Section 17.1.7.

The observed values of SDS total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in SDS total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 4E) and LOCF.

17.1.8. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN EQ-5D-5L VAS AND INDEX SCORES AT EACH SCHEDULED VISIT

The EuroQol-5 Dimensions – 5 Levels (EQ-5D-5L) is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of two parts: a) the EQ-5D-5L descriptive system, and b) the EQ VAS.

The EQ-5D-5L descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: level 1 (no problems), level 2 (slight problems), level 3 (moderate problems), level 4 (severe problems), and level 5 (extreme problems/unable to do). The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension (i.e., the index score).

The index scores for the five dimensions can be combined into a 5-digit code that describes the patient's health state. An index value (a weighted scoring of the 5 dimension scores with a possible range from less than 0 [where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead] to 1 [the value of full health]) will be assigned to each observed health state using the US standard value set as defined in APPENDIX 3.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale from 0 to 100, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgment.

EQ-5D-5L is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The DB Baseline and OL Baseline EQ-5D-5L VAS and Index scores will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in EQ-5D-5L VAS and Index scores will be derived as described in Section 17.1.8.

The observed values of EQ-5D-5L VAS and Index scores at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in EQ-5D-5L VAS and Index scores will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 4E) and LOCF.

17.1.9. CHANGES FROM DB BASELINE AND FROM OL BASELINE IN SHAPS TOTAL SCORE AT EACH SCHEDULED VISIT

The Snaith-Hamilton Pleasure Scale (SHAPS) is a subject-reported questionnaire having a 14-item scale that assesses 4 domains of hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink. Each of the items has a set of four response categories: strongly disagree, disagree, agree, or strongly agree, with either of the Disagree responses receiving a score of 1 and either of the Agree responses receiving a score of 0. Thus, the SHAPS total score is scored as the sum of the 14 items and ranges from 0 to 14. A higher SHAPS total score indicated higher levels of present state of anhedonia.

SHAPS is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The DB Baseline and OL Baseline SHAPS total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in SHAPS total score will be derived as described in Section 17.1.9.

The observed values of SHAPS total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in SHAPS total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 4E) and LOCF.

17.2. MISSING DATA

Any individual missing item in any scale will not be imputed.

For derived scores that depend on more than one individual item (e.g., MADRS total score, EQ-5D-5L index score), if one or more items are missing at a visit, the derived score will be set to missing. The corresponding change from DB Baseline or OL Baseline value at a given time point will be set to missing if the DB Baseline or OL Baseline derived score is missing or if the derived score at that time point is missing.

For MADRS response compared to DB Baseline, any subject with a missing MADRS total score at DB Baseline or at any scheduled OLE study visit (starting from Visit 1E) or LOCF will have their MADRS response set to missing for that time point.

18. SAFETY OUTCOMES

Unless otherwise specified, the safety summary tables will include the following columns: PBO-SEP, SEP-SEP, and ALL EXT (all rollovers from SEP380-301).

All analyses of the safety outcomes will be based on the Safety Population, by the actual treatment groups.

18.1. ADVERSE EVENTS

Adverse Events (AEs) and pre-treatment events will be coded using MedDRA central coding dictionary, Version 22.0.

The concept of “pre-treatment events” only applies to study SEP380-301. Pre-treatment events are untoward medical occurrences that started prior to the first dose of study medication in SEP380-301.

Adverse events of study SEP380-301 are untoward medical occurrences that started at the same time of or after the first dose of study medication in SEP380-301, but before the first dose of OLE study medication in SEP380-303. These events will be recorded in the SEP380-301 databases.

Adverse events (AEs) of the SEP380-303 extension study are untoward medical occurrences that started at the same time of or after the first dose of the OLE study drug. These events will be recorded in the SEP380-303 database.

AEs (and pre-treatment events) that started in study SEP380-301 and are ongoing at the time of subject rollover will be re-entered into the SEP380-303 database and continue to be followed. These events will not be included in any AE summary table of SEP380-303. They will only be listed in a separate data listing.

Whenever available, the time information should be accounted for to determine if a record in the SEP380-303 AE database belongs to study SEP380-301 or SEP380-303. In the case where time is not available, untoward medical occurrences that started prior to the day of the first OLE dose will be considered to belong to study SEP380-301; those that started after the day of the first OLE dose will be considered to belong to study SEP380-303. Events that started on the same day of the first OLE dose will be assigned to study SEP380-301 or SEP380-303 depending on whether this AE record also exists in the SEP380-301 database (based on a comparison of subject ID, verbatim term, AE start date (and time if available), severity, and seriousness.

See APPENDIX 2 for handling of partial dates for AEs.

Overall summary of the incidence of all AEs, study medication-related AEs, severe AEs, serious AEs, AEs leading to discontinuation from study, AEs leading to death, and AEs of special interest (AESI) will be provided by the actual treatment groups.

Listings will be provided for all AEs, study medication-related AEs, severe AEs, serious AEs, AEs leading to discontinuation from the study, AEs leading to death, and AEs of special interest (AESI). A listing of SEP380-301 events (pre-treatment events and AEs) present in the SEP380-303 database will also be presented. When complete event start date and complete event end date are available, duration of AEs from SEP380-301/303 and pre-treatment events from SEP380-301 will be calculated as: event end date – event start date + 1. Duration will be presented in data listings.

For all summaries, each subject will be counted only once within each category (e.g., an AE type, a severity level, a relationship category, a SOC, and a PT). If not otherwise specified, all summaries will present the number and percentage of subjects as well as the number of events. For summaries by SOC and PT, AEs will be sorted by SOC based on the internationally agreed order (see APPENDIX 4) and then by PT in decreasing frequency in the “ALL EXT” column. For summaries by SOC, and PT, AEs will be sorted by SOC based on the internationally agreed order and then by PT in decreasing frequency in the “ALL EXT” column.

18.1.1. ALL AEs

All AEs will be summarized by PT, as well as by SOC and PT.

In addition, summary tables (by SOC and PT) will be generated for those AEs starting after the last dose of OLE study drug and those AEs starting more than 1 day after the last dose of OLE study drug.

The summary by SOC and PT will be broken down further by maximum severity and by strongest relationship to study medication. These summaries are described in the sections below.

18.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). AEs with a missing severity will be classified as severe.

If a subject reported an AE more than once within the same SOC/ PT with different severity levels, the

subject will be assigned to a severity level for that SOC/ PT based on the worst case severity (i.e., maximum severity). Event counts will not be included in this summary.

In a separate table, severe AEs will be summarized by SOC and PT.

18.1.1.2. Relationship to study medication

Relationship to study medication, as indicated by the Investigator, is classed as “not related”/ “possible”/ “probable”/ “definite” (increasing strength of relationship). A “related” AE is defined as an AE with a relationship to study medication as “possible”, “probable” or “definite”. AEs with a missing relationship to study medication will be regarded as related to the study medication. For this summary, AEs will be presented in 2 categories, related and not related.

If a subject reported an AE more than once within the same SOC/ PT in different relationship categories, the subject will be assigned to a category for that SOC/ PT based on the worst case relationship (i.e., strongest relationship). Event counts will not be included in this summary.

18.1.2. AEs Leading to Discontinuation from Study

AEs leading to discontinuation from the study are those AEs with “Caused Study Discontinuation” = “Yes” on the “*Adverse Events*” CRF form for subjects with reason for discontinuation as AE on the Study Disposition CRF page or AE action taken = ”Drug Withdrawn”.

AEs leading to discontinuation from the study will be summarized by SOC and PT. A listing of AEs leading to discontinuation from the study treatment period will be presented.

18.1.3. Serious Adverse Events (Including Adverse Events Leading to Death)

SAEs are those AEs recorded as ”Serious” on the “*Adverse Events*” CRF form. AEs leading to death are those AEs with “Outcome” = ”Fatal” on the “*Adverse Events*” CRF form.

SAEs (including AEs leading to death) will be summarized by SOC and PT. A listing of SAEs (including deaths) will be presented.

18.1.4. Adverse Events of Special Interest (AESI)

A list of preferred terms that are to be combined for assessment of adverse events of special interest (AESI), eg, hyperprolactinemia-related AEs, details of definition are provided in Appendix 5.

AEs potentially associated with the study medication SEP-4199 CR:

- Extrapyramidal symptoms (EPS): SMQ Extrapyramidal symptoms and 4 sub-classes (broad),
- QT prolongation: SMQ Torsade de Pointes/QT prolongation (narrow, broad),

AESI will be summarized by AESI category and preferred term for overall subjects.

18.2. Laboratory Evaluations

Results from the central laboratory to be reported for this study include Hematology, Chemistry (including lipid panel and thyroid panel), Urinalysis, Urine drug screening, Serum pregnancy (β-HcG) (in

female subjects only), and Urine pregnancy (in female subjects only).

Serum and urine pregnancy results in female subjects and any unexpected lab parameters not specified in protocol Section 21 (APPENDIX II. CLINICAL LABORATORY TESTS) will only be listed. Laboratory parameters prespecified in protocol Section 21 under the categories of "HEMATOLOGY", "BLOOD CHEMISTRIES" (plus HOMA-IR), "URINALYSIS", and "URINE DRUG SCREENING will be summarized in tables as well as presented in listings.

Listing presentations will use both standard international (SI) Units and conventional units. Table summaries will also be provided using both SI units and conventional 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 they will be presented as recorded, i.e., as "< X" or "> X" in the listings.

The following summaries will be provided:

- For quantitative measurements in hematology, chemistry, and urinalysis: By-visit summary of observed values at DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E), and LOCF; by-visit summary of change from DB Baseline at each scheduled OLE study visit (starting from Visit 1E) and LOCF; by-visit summary of change from OL Baseline at each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

Serum prolactin results will be summarized overall and separately by sex. Glucose, insulin, HOMA-IR, and lipid panel results (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) will be summarized by fasting status: fasting only and overall (fasting, non-fasting, or fasting status unknown combined).

Change from DB Baseline for glucose, insulin, HOMA-IR, and lipid panel results will only be calculated if the fasting status at a given OLE study visit is matching the fasting status at DB Baseline. Change from OL Baseline will only be calculated if the fasting status at a given post-OL Baseline extension study visit is matching the fasting status at OL Baseline.

- For qualitative measurements in urinalysis (as applicable) and for urine drug screening results: By-visit summary of the number and percentage of subjects in each outcome category at DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E), and LOCF. Urine drug screening results will be reported as "Positive"/ "Negative".

- Shift in laboratory results (chemistry, hematology, urinalysis) from DB Baseline to each scheduled OLE study visit (starting from Visit 1E) and LOCF, and shift from OL Baseline to each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF, according to the reference range criteria.

The existing reference range indicators provided by the central laboratory will be mapped as needed to categories of "Normal" (within the reference range) / "Abnormal" (outside the reference range) for urinalysis non-pH results, and to categories of "Low" (below the reference range) / "Normal" (within the reference range) / "High" (above the reference range) for chemistry and hematology results as well as urinalysis pH results.

- Number and percentage of subjects with at least one potentially clinically significant (PCS) laboratory value (see APPENDIX 6) post-OL Baseline. The period of evaluation includes both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose, including unscheduled visits. Subjects will be counted in a particular PCS category if they met that PCS criteria at least once during the period of evaluation, regardless of their DB or OL Baseline value.

All laboratory data will be provided in data listings, with the values outside the reference ranges flagged. In addition, separate listings will be provided to present the laboratory data that met the PCS criteria.

18.2.1. LABORATORY SPECIFIC DERIVATIONS

- Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) will be calculated for each visit:

HOMA IR = Glucose (mg/dL) × Insulin (mU/L) / 405

The following conversion factors will be used if needed:

Glucose (mg/dL) = Glucose (mmol/L) × 18.015588;

Insulin (mU/L) = Insulin (pmol/L) × (1/6).

18.2.2. LABORATORY REFERENCE RANGES

Laboratory reference range indicators will be provided by the laboratory vendor and 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 laboratory parameters with categorical outcomes 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”.

18.3. ECG EVALUATIONS

Data from the centrally over-read ECG (Electrocardiogram) results will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- RR Interval (msec)
- QRS Duration (msec)
- QRS Axis (deg)
- QT Interval (msec)
- QTcF Interval (msec) (Fridericia’s Correction of QT interval)
- QTcB Interval (msec) (Bazett’s Correction of QT interval)

- Heart Rate (bpm)

- Overall assessment of ECG as determined by the central over-read:

o Normal
o Abnormal, Insignificant
o Abnormal, Potentially Significant
o Abnormal, Significant
o Exclusion Alert (only given for the Screening visit of core study). In table summaries, the category of "Exclusion Alert" will be combined into the category of "Abnormal, Significant".
o Not Evaluable

- ECG findings

ECG findings will only be listed. Other ECG data will be summarized in tables as well as presented in listings.

The following summaries will be provided:

- For quantitative measurements: By-visit summary of observed values at DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E, Visit 1EJ for Japan subjects), and LOCF; by-visit summary of change from DB Baseline at each scheduled OLE study visit (starting from Visit 1E) and LOCF; by-visit summary of change from OL Baseline at each scheduled post-OL Baseline extension study visit (starting from Visit 2E, Visit 1EJ for Japan subjects) and LOCF.

- For ECG overall assessment results as determined by the central over-read ("Normal", "Abnormal, not Clinically Significant (NCS)", "Abnormal, Clinically Significant (CS)", "Not Evaluable"): By-visit summary of number and percentage of subjects in each category at DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E, Visit 1EJ for Japan subjects), and LOCF.

- Shift in ECG overall assessment as determined by the central over-read from DB Baseline to each scheduled OLE study visit (starting from Visit 1E) and LOCF, and shift from OL Baseline to each post-OL Baseline extension study visit (starting from Visit 2E, Visit 1EJ for Japan subjects) and LOCF.

- Number and percentage of subjects who met each of the QTc interval prolongation criteria (see Section 18.3.1) considering both DB Baseline and OL Baseline. The period of evaluation includes both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose, including unscheduled visits.

- Number and percentage of subjects with at least one PCS ECG value (see Table 3 in Section 18.3.1) post-OL Baseline. The period of evaluation includes both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose, including unscheduled visits. Subjects will be counted in a particular PCS category if they met that PCS criteria at least once during the period of evaluation, regardless of their OL or DB Baseline value.

All ECG parameters, overall assessment as determined by the central over-read, and findings will be provided in a data listing. In addition, separate listings will be generated to present the QTc interval data of subjects who met at least one QTc prolongation criterion and the ECG data that met the PCS criteria.

18.3.1. ECG POTENTIALLY CLINICALLY SIGNIFICANT CRITERIA

QTc interval prolongation in adult subjects will be identified in accordance with the following predefined Potentially clinically significant criteria (same criteria apply to both QTcF and QTcB):

- > 450 msec for males \ > 470 msec for females at any post-OL Baseline time point (including unscheduled visits) not present at DB Baseline
- > 450 msec for males \ > 470 msec for females at any post-OL Baseline time point (including unscheduled visits) not present at OL Baseline
- > 480 msec at any post-OL Baseline time point (including unscheduled visits) not present at DB Baseline
- > 480 msec at any post-OL Baseline time point (including unscheduled visits) not present at OL Baseline
- > 500 msec at any post-OL Baseline time point (including unscheduled visits) not present at DB Baseline
- > 500 msec at any post-OL Baseline time point (including unscheduled visits) not present at OL Baseline
- ≥ 30 msec increase from DB Baseline for at least one post-OL Baseline measurement (including unscheduled visits) and < 60 msec increase from DB Baseline for all post-OL Baseline measurements (including unscheduled visits)
- ≥ 30 msec increase from OL Baseline for at least one post-OL Baseline measurement (including unscheduled visits) and < 60 msec increase from OL Baseline for all post-OL Baseline measurements (including unscheduled visits)
- ≥ 60 msec increase from DB Baseline for at least one post-OL Baseline measurement (including unscheduled visits)
- ≥ 60 msec increase from OL Baseline for at least one post-OL Baseline measurement (including unscheduled visits)

Except for the potentially clinically significant QTc criteria as described above, the PCS ECG measurements will be identified in accordance with the following predefined PCS criteria:

Table 3: Predefined ECG PCS criteria.

ECG Parameter	PCS Low	PCS High
Heart Rate (beats/min)	< 50	> 100
PR Interval (msec)	--	> 210
QRS Interval (msec)	--	> 120

18.4. VITAL SIGNS

The following vital sign measurements will be reported for this study:

- Supine and Standing Systolic Blood Pressure (mmHg)
- Supine and Standing Diastolic Blood Pressure (mmHg)

- Supine and Standing Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{o}C)
- Weight (kg)
- BMI (kg/m^2)
- Waist Circumference (cm)

Height will be summarized as part of the Baseline characteristics only.

The following summaries will be provided:

- By-visit summary of observed values at DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E), and LOCF; by-visit summary of change from DB Baseline at each scheduled OLE study visit (starting from Visit 1E) and LOCF; by-visit summary of change from OL Baseline at each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.
- Number and percentage of subjects with at least one PCS vital sign value (see Section 18.4.2) post-OL Baseline. The period of evaluation includes both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose, including unscheduled visits. Subjects will be counted in a particular PCS category if they met that PCS criteria at least once during the period of evaluation, regardless of their DB Baseline or OL Baseline value.
- Number and percentage of subjects with orthostatic hypotension and/or orthostatic tachycardia (see Section 18.4.1). The data will be summarized for DB Baseline, OL Baseline, overall post-OL Baseline extension period (which covers both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose, including unscheduled visits), each scheduled OLE study visit (starting from Visit 2E), and LOCF.
- By-visit summary of BMI category (see Section 12) at DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E), and LOCF.

All vital signs data will be provided in a data listing. In addition, a separate listing will be generated to present the vital signs data that met the PCS criteria. All occurrences of orthostatic hypotension and orthostatic tachycardia will also be presented in a listing.

18.4.1. VITAL SIGNS SPECIFIC DERIVATIONS

- BMI expressed in kg/m^2 = Weight (kg)/ [height (cm)/100]^2.

The height collected at Visit 1 in SEP380-301 will be used to derive BMI where needed throughout the study.

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

- Orthostatic tachycardia is defined as a heart rate increase of ≥ 20 bpm after a subject has been standing for at least 2 to 4 minutes compared to the heart rate measured in the supine position, and a heart rate of > 100 bpm after the subject has been standing for at least 2 to 4 minutes.

18.4.2. VITAL SIGN POTENTIALLY CLINICALLY SIGNIFICANT CRITERIA

Potentially clinically significant vital sign measurements will be identified in accordance with the following predefined PCS criteria, considering both DB Baseline and OL Baseline:

Table 4: Predefined vital sign PCS criteria

Vital Sign Parameter	PCS Low	PCS High
Systolic Blood Pressure (Supine, Standing) (mmHg)	Value ≤ 90 and ≥ 20 decrease from DB/OL Baseline	Value ≥ 180 and ≥ 20 increase from DB/OL Baseline
Diastolic Blood Pressure (Supine, Standing) (mmHg)	Value ≤ 50 and ≥ 15 decrease from DB/OL Baseline	Value ≥ 105 and ≥ 15 increase from DB/OL Baseline
Pulse Rate (Supine, Standing) (beats/min)	Value ≤ 50 and ≥ 15 decrease from DB/OL Baseline	Value ≥ 120 and ≥ 15 increase from DB/OL Baseline
Respiration Rate (breaths/min)	Value ≤10 and ≥ 50% decrease from DB/OL Baseline	Value ≥ 25 and ≥ 50% increase from DB/OL Baseline
Weight (kg)	≥ 7% decrease from DB/OL Baseline	≥ 7% increase from DB/OL Baseline
Temperature (°C)	NA	Value ≥ 38.3°C and ≥ 0.8°C increase from DB/OL Baseline

18.5. PHYSICAL EXAMINATION

As all physical and neurological findings will be recorded as AEs, no specific analysis of physical and neurological examination will be performed.

18.6. OTHER SAFETY ASSESSMENTS

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

The C-SSRS is a tool designed to systematically assess and track suicidal behavior and suicidal ideation 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 of studies SEP380-301. The C-SSRS Since Last Visit Version is used from Visit 2 and onward in studies SEP380-301, and at all visits in extension study SEP380-303. 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 two main sections: Suicidal Ideation and Suicidal Behavior.

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

in the presentation of the results.

- Suicidal ideation is measured by 5 categories, representing 5 subtypes of suicidal ideation with increasing severity:

  - 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

- Suicidal behavior is measured by 5 categories, representing 5 subtypes of suicidal behavior:

  - 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 10 categories above are mutually exclusive. Subjects will be counted in the most severity 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).

For the purpose of C-SSRS analysis, “DB Baseline”, “OL Baseline”, and the overall “post-OL Baseline Extension” periods are defined as follows.

Time point	**Study Visit**	**C-SSRS Version**	**Derivation Rule**
DB Baseline	Visit 1 of study SEP380-301	Baseline/Screening – Past 1 Month for Suicidal Ideation / Past 6 Months for Suicidal Behavior	Most severe outcome
	Visit 2* of study SEP380-301	Since Last Visit	
OL Baseline	Week 6/Visit 6** of study SEP380-301	Since Last Visit	As collected for that visit
Post-OL Baseline Extension Period	All post-OL Baseline extension study visits up to and including 7 days post the last OLE dose, including unscheduled visits	Since Last Visit	Most severe outcome

* Note: The Visit 2 C-SSRS assessment must be administered prior to the first dose of SEP380-301 study medication in order to be used in the C-SSRS DB Baseline derivation.

**Note: The Visit 6 C-SSRS assessment must be administered prior to the first dose of SEP380-303 extension study medication in order to be used as the C-SSRS OL Baseline. In the rare event where the Visit 6 assessment is administered after the first dose of SEP380-303 extension study medication, take the assessment from the previous visit as the OL Baseline.

The following C-SSRS composite endpoints will be derived for each time point of interest (i.e., DB Baseline, OL Baseline, overall post-OL Baseline extension period, and each OLE 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 behavior questions on the C-SSRS (Categories 1-10).

For each subject, the suicidal ideation score at each time point of interest (i.e., DB Baseline, OL Baseline, overall post-OL Baseline extension period, each OLE study visit, and LOCF) is defined as the maximum suicidal ideation category (1-5) present for the time point of interest. If no ideation is present a score of 0 is assigned.

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

- DB Baseline (as defined above)
- OL Baseline (as defined above)
- Overall post-OL Baseline extension period (as defined above)
- Each scheduled OLE study visit (starting from Visit 2E)

Shift in suicidal ideation score from DB Baseline to the overall post-OL Baseline extension period, each scheduled OLE study visit (starting from Visit 1E), and LOCF, and shift from OL Baseline to each scheduled post-OL Baseline extension study visit (starting from Visit 2E), and LOCF, will be presented.

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'.

Responses to each C-SSRS question will be listed. The ideation intensity total score and the actual lethality and potential lethality of actual attempts will only be presented in data listings.

18.6.2. YOUNG MANIA RATING SCALE (YMRS)

The YMRS will be administered as a safety assessment and to inform the identification of treatment-emergent mania or hypomania.

The YMRS is a clinician-rated 11-item instrument used to assess the severity of mania in subjects with a diagnosis of bipolar disorder. The 11 items assess: Elevated Mood, Increased Motor Activity/Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language/Thought Disorder, Content, Disruptive-Aggressive Behavior, Appearance, and Insight. The YMRS total score is the sum of the 11 individual items and ranges from 0 to 60. A higher score is associated with a greater severity of mania.

If one or more items are missing at a visit, the total score will be set to missing.

YMRS is assessed at Week 2 and monthly and at these study visits: from Visit 1E (coinciding with Visit 6 of SEP380-301) to Visit 15E.

Treatment-emergent mania or hypomania is defined as a YMRS total score ≥ 16 at any 2 consecutive post-OL Baseline visits or at the final visit, or an AE of mania or hypomania during the post-OL Baseline extension period (including both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose).

The DB Baseline and OL Baseline YMRS total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in YMRS total score will be derived as described in Section 7.7.

The observed values of YMRS total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 2E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in YMRS total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

Frequency and percentage of subjects experiencing treatment-emergent mania at any time during the study will be presented by treatment group.

18.6.3. ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. It contains seven items related to: facial, lip, jaw, and tongue movements (items 1 - 4), upper and lower extremity movements (items 5 - 6), and trunk movements (item 7). Three other items assess the subject at a global level (items 8 - 10), and two items assess dental status (items 11 - 12).

AIMS is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 2E, Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The (non-global) AIMS total score is the sum of items 1 through 7. (Items 8 through 12 are not used in AIMS total score calculation.) The possible range for AIMS total score is 0 to 28. Higher values of the AIMS total score indicate increased severity in abnormal movement. If one or more of the 7 items contributing to AIMS total score calculation are missing at a visit, the total score will be set to missing for that visit.

AIMS total score at each visit is classified as ‘abnormal’ if: either at least two items (out of items 1 - 7) have a response of ‘Mild’ or higher (i.e., item score ≥ 2); or at least one item (out of items 1 - 7) has a response of ‘Moderate’ or higher (i.e., item score ≥ 3). Otherwise, the non-missing AIMS total scores is classified as ‘normal’.

Item 8 of AIMS represents the global severity score. Post-Baseline AIMS global severity scores will be classified as ‘worsened’, ‘unchanged’, or ‘improved’, relative to a subject’s Baseline response to item 8. A higher score than that of the Baseline would be classified as ‘worsened’. Conversely, a lower score would be classified as ‘improved’. If the score is equal to that of Baseline, the score will be classified as ‘unchanged’. Relative to DB Baseline, the classification will be made for each OLE study visit. Relative to OL Baseline, the classification will be made for each post-OL Baseline extension study visit.

The DB Baseline and OL Baseline AIMS total score and global severity score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in AIMS total score and global severity score will be derived as described in Section 7.7.

The observed values of AIMS total score and global severity score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 2E) and LOCF, will be summarized

descriptively.

Changes from DB Baseline in AIMS total score and global severity score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

Shift in AIMS total score category (Normal/Abnormal) from DB Baseline to each scheduled OLE study visit (starting from Visit 1E), LOCF, and the overall post-OL Baseline extension period (including both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose) will be summarized descriptively. Similarly, shift from OL Baseline in AIMS total score category to each scheduled post-OL Baseline extension study visit (starting from Visit 2E), LOCF, and the overall post-OL Baseline extension period will be summarized descriptively.

Frequency distribution of the AIMS global severity item will be summarized descriptively for DB Baseline, OL Baseline, each scheduled OLE study visit (starting from Visit 2E), and LOCF.

Changes in AIMS global severity score relative to DB Baseline (Worsened/Unchanged/Improved) will be summarized descriptively for each scheduled OLE study visit (starting from Visit 1E) and LOCF; changes relative to OL Baseline will be summarized descriptively for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

18.6.4. 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 (item 1), two items targeting subjective restlessness (awareness and related distress; items 2 - 3), and one global clinical assessment of akathisia item (item 4). The objective and subjective items are anchored and utilize a 4-point scale. The global assessment item has a 6-point scale (from absence of akathisia through severe akathisia).

BARS is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 2E, Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The BARS total score is the sum of items 1 through 3 and ranges from 0 to 9. Higher values of the BARS total score indicate higher severity of akathisia. If one or more of items 1 to 3 are missing at a visit, the BARS total score will be set to missing for that visit.

The post-Baseline BARS Global Clinical Assessment of Akathisia responses will be classified as ‘worsened’, ‘unchanged’, or ‘improved’, relative to a subject’s Baseline response to this item. A higher score than that of the Baseline would be classified as ‘worsened’. Conversely, a lower score would be classified as ‘improved’. If the score is equal to that of Baseline, the score will be classified as ‘unchanged’. Relative to DB Baseline, the classification will be made for each OLE study visit. Relative to OL Baseline, the classification will be made for each post-OL Baseline extension study visit.

The DB Baseline and OL Baseline BARS total score and BARS item scores will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in BARS total score and BARS item scores will be derived as described in Section 7.7.

The observed values of BARS total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 2E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in BARS total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

Changes in BARS global clinical assessment score relative to DB Baseline (Worsened/Unchanged/Improved) will be summarized descriptively for each scheduled OLE study visit (starting from Visit 1E) and LOCF; changes relative to OL Baseline will be summarized descriptively for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

18.6.5. MODIFIED SIMPSON-ANGUS SCALE (MSAS)

The MSAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale (ranging between 0 and 4), and address rigidity, gait (bradykinesia), tremor, akathisia, shoulder shaking, glabellar tap, and salivation.

MSAS total score is defined as the sum of all 10 items and ranges between 0 and 40. Lower values of the MSAS total score indicate milder symptoms. If one or more of the MSAS items are missing at a visit, the MSAS total score will be set to missing for that visit.

The MSAS total score at each visit will be classified as 'abnormal' if it exceeds 3 (Rush, et al., 2000). Otherwise, the non-missing MSAS total score will be classified as 'normal'.

MSAS is assessed at these study visits: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 2E, Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E.

The DB Baseline and OL Baseline MSAS total score will be derived as described in Section 7.2. The change from DB Baseline and OL Baseline in MSAS total score will be derived as described in Section 7.7.

The observed values of MSAS total score at both the DB Baseline and the OL Baseline, and at each scheduled OLE study visit (starting from Visit 1E) and LOCF, will be summarized descriptively.

Changes from DB Baseline in MSAS total score will be summarized for each scheduled OLE study visit (starting from Visit 1E) and LOCF. Changes from OL Baseline will be summarized for each scheduled post-OL Baseline extension study visit (starting from Visit 2E) and LOCF.

Shift in MSAS total score category (Normal/Abnormal) from DB Baseline to each scheduled OLE study visit (starting from Visit 1E), LOCF, and the overall post-OL Baseline extension period (including both the OLE treatment period and the OLE follow-up period up to and including 7 days post the last OLE dose) will be summarized descriptively. Similarly, shift from OL Baseline in MSAS total score category to each scheduled post-OL Baseline extension study visit (starting from Visit 2E), LOCF, and the overall post-OL Baseline extension period will be summarized descriptively.

18.6.6. PHYSICIAN'S WITHDRAWAL CHECKLIST (PWC)

Potential withdrawal effects will be assessed by the clinician using the PWC after completion of all scheduled effectiveness and safety assessments and procedures at Visit 14E (EOT/ET) and Follow-up (Visit 15E).

The PWC scale includes 20 symptoms and each symptom is assessed on a 4 point scale using the following: 0=Not Present, 1=Mild, 2=Moderate and 3=Severe. The score for each question is summed to compute a total score ranging from 0 to 60. If the response to any question is missing, then the total score will be missing.

The PWC total score will be summarized using descriptive statistics by visit and treatment group.

The frequency distribution of the PWC will be tabulated at Visit 14E and Follow-up.

19. PHARMACOKINETIC ANALYSIS

All PK analysis will be performed using Safety population.

Blood sample for plasma concentrations of R-amisulpride, S-amisulpride, total amisulpride, and/or plasma prolactin measurement will be collected at: Visit 1E (coinciding with Visit 9 of SEP380-301), Visit 2E, Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, Visit 14E, and Visit 15E/Follow-up. Any plasma concentration or summary statistics below the lower limit of quantification (LLOQ) will be represented by "BLQ" (below the limit of quantification) in tables and listings. Amisulpride plasma concentration will not

be presented for the placebo group.

R-amisulpride, S-amisulpride, total amisulpride, and plasma prolactin concentrations at each scheduled sample collection time point (including ET and Follow-up, see Section 7.4 for mapping of the ET visit) will be summarized descriptively (n, mean, median, minimum, maximum, coefficient of variation [CV] and if appropriate, geometric mean and geometric CV [GCV]). In addition, if there is at least 1 concentration < LLOQ within a treatment group at a time point, it will be set to ½ LLOQ for summary statistics calculations. Number and percentage of concentrations that are below the LLOQ will be provided for each visit. All PK summaries will be presented.

Population PK analysis methods will be used to characterize the PK/PD profiles in subjects treated with SEP-4199 CR. Analysis methods and results of population PK and PD analysis will be described in a separate document from the SAP and clinical study report.

19.1. DERIVATION

LLOQ is 0.0500 ng/mL for R-amisulpride and S-amisulpride and LLOQ is 1.56 ng/mL for plasma prolactin.

Below derivations apply after concentrations lower then LLOQ are set to ½ LLOQ.

- Coefficient of variation

  100*Standard Deviation/Mean

- Geometric Mean

  Exponential (mean of $\log_e$ transformed data)

- Geometric CV

  Square Root (Exponential (Variance ($\log_e$ transformed data)-1))*100

20. DATA NOT SUMMARIZED OR PRESENTED

The variables and/or domains not summarized or presented are:

- Subject initials.

21. REFERENCES

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Rush, A., Pincus, H., First, M., Blacker, D., Endicott, J., Keith, S., . . . Zarin, D. (2000). *Handbook of Psychiatric Measures.* American Psychiatric Association.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Where applicable, the Appendix_compilation_working_update_2022Final.pdf document – provided by SMPA – will be followed.

In addition, the following output conventions are to be followed:

- General presentation:
  - The left-hand column should start in column 1. No centering of the output should occur.
  - Rounding should be done with the SAS function ROUND.
  - Numbers in tables should be rounded, not truncated.
  - Alphanumeric output should be left aligned.
  - Numbers should be decimal point aligned.
  - Whole numbers should be right aligned.
  - Text values should be left aligned.
  - The first letter of a text entry should be capitalized.
- Univariate Statistics: If the raw data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum and maximum: N
  - Mean, median, Q1, and Q3: N + 1
  - SD: N + 2
- Frequencies and percentages (n and %):
  - Percent values should be reported inside parentheses, with one space between the count (n) 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.
  - Percentages will be reported to one decimal place, except cases where percent < 100.0% but > 99.9% will be presented as '> 99.9%' (e.g., 99.99% is presented as > 99.9%); and cases where percent < 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.
  - Where counts are zero, no percentage should appear in the output.
- Confidence Intervals:
  - Confidence intervals and estimates are presented to one place more than the raw data, 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.
- Ratios should be reported to one more decimal place than the raw data.
- Spacing must be a minimum of 1 blank space between columns (preferably 2).
- 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.

- Figures:

  - Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
  - The image should be clear and of high quality when viewed in the Word document, and when printed.
  - In general, boxes around the figures should be used.

- Footers should be defined as follows:

  - A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page.
  - Table footnotes should appear directly after the body of the table.
  - If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.

DATES & TIMES

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

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment sequences will be represented as follows and in that order:

Treatment Sequence	For Tables (Column Order)	For Graphs (Order)
Placebo - SEP-4199 CR	PBO-SEP (1)	PBO-SEP (2)
SEP-4199 CR 200 mg/day - SEP-4199 CR	SEP-SEP (2)	SEP-SEP (3)
SEP-4199 CR 400 mg/day - SEP-4199 CR	SEP-SEP (2)	SEP-SEP (3)
	ALL-EXT (3)	ALL EXT (1)

LISTINGS

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

- Subject ID.
- Visit (where applicable)
- Original date/time (where applicable).

APPENDIX 2. PARTIAL DATE CONVENTIONS

The actual dates as collected on the CRF will be presented in the listings. Imputed dates will NOT be presented in the listings unless otherwise specified.

ALGORITHM FOR ADVERSE EVENTS

The algorithm below applies to all SEP380-301/303 AEs and SEP380-301 pre-treatment event records collected in the SEP380-303 clinical database.

Step 1) For events that exist in the SEP380-301 databases and have a missing or partial start date, retrieve imputed event start dates from the respective ADaM dataset.

Events in the SEP380-303 database which also exist in the SEP380-301 databases will be identified based on a comparison of subject ID, PT, AE start date (and time if available), severity, and seriousness.

Step 2) For events that do not exist in the SEP380-301 databases yet the known part of the event start and/or end dates show that the event unambiguously started before first OLE dose in SEP380-303, impute missing or partial event start and/or end dates (if not ongoing) using the algorithm below.

If an event has some missing components in both the start and end dates, first impute the end date.

AE end date imputation

- If year and month (YYYY-MM) of AE end date are known, then impute the missing day to be the earlier of (last day of the month; date of SEP380-301 last contact).
- If only year (YYYY) of AE end date is known, then impute the missing month and day to be the earlier of (31st December; date of SEP380-301 last contact).
- If AE end date is completely missing and AE is not ongoing, then impute AE end date to be date of SEP380-301 last contact.

AE start date imputation

- If year and month (YYYY-MM) of AE start date are known and YYYY-MM = year and month of SEP380-301 study med start date, then impute AE start date to be the earlier of (SEP380-301 study med start date; full or imputed AE end date [if non-missing]).
- If year and month (YYYY-MM) of AE start date are known and YYYY-MM ≠ year and month of SEP380-301 study med start date, then impute AE start date to be YYYY-MM-01.
- If only year (YYYY) of AE start date is known and YYYY = year of SEP380-301 study med start date, then impute AE start date to be the earlier of (SEP380-301 study med start date; full or imputed AE end date [if non-missing]).
- If only year (YYYY) of AE start date is known and YYYY ≠ year of SEP380-301 study med start date, then impute AE start date to be YYYY-01-01.
- If AE start date is completely missing, then impute AE start date to be the earlier of (SEP380-301 study med start date; full or imputed AE end date [if non-missing]).

Step 3) For the remaining events in SEP380-303 database, impute missing or partial event start and/or end dates (if not ongoing) using the algorithm below.

If an event has some missing components in both the start and end dates, first impute the end date.

AE end date imputation

- If year and month (YYYY-MM) of AE end date are known, then impute the missing day to be the earlier of (last day of the month; date of SEP380-303 last contact).
- If only year (YYYY) of AE end date is known, then impute the missing month and day to be the earlier of (31st December; date of SEP380-303 last contact).
- If AE end date is completely missing and AE is not ongoing, then impute AE end date to be date of SEP380-303 last contact.

AE start date imputation

- If year and month (YYYY-MM) of AE start date are known and YYYY-MM = year and month of OLE study med start date, then impute AE start date to be the earlier of (OLE study med start date; full or imputed AE end date [if non-missing]).
- If year and month (YYYY-MM) of AE start date are known and YYYY-MM ≠ year and month of OLE study med start date, then impute AE start date to be YYYY-MM-01.
- If only year (YYYY) of AE start date is known and YYYY = year of OLE study med start date, then impute AE start date to be the earlier of (OLE study med start date; full or imputed AE end date [if non-missing]).
- If only year (YYYY) of AE start date is known and YYYY ≠ year of OLE study med start date, then impute AE start date to be YYYY-01-01.
- If AE start date is completely missing, then impute AE start date to be the earlier of (OLE study med start date; full or imputed AE end date [if non-missing]).

Step 4) Using the full or imputed event dates, assign events into SEP380-301 pre-treatment event, SEP380-301 AE, or SEP380-303 AE as described below.

If both event start date/time and SEP380-303 OLE study med start date/time are available:

- If event start date/time < SEP380-303 OLE study med start date/time, then SEP380-301 pre-treatment event or SEP380-301 AE*.
- If event start date/time ≥ SEP380-303 OLE study med start date/time, then SEP380-303 AE.

If (event start date is avaialble and time is not avaialble) and/or (SEP380-303 OLE study med start date is avaialble and time is not avaialble):

- If event start date < SEP380-303 OLE study med start date, then SEP380-301 pre-treatment event or SEP380-301 AE*.
- If event start date > SEP380-303 OLE study med start date, then SEP380-303 AE.
- If event start date = SEP380-303 OLE study med start date and the event record exists in SEP380-301 database§, then SEP380-301 pre-treatment event or SEP380-301 AE*.
- If event start date = SEP380-303 OLE study med start date and the event record does not exist in SEP380-301 database§, then SEP380-303 AE.

*The distinction between SEP380-301 pre-treatment event and SEP380-301 AE should be performed as specified in the SEP380-301 SAP.

§Based on a comparison of subject ID, PT, AE start date (and time if available), severity, and seriousness.

ALGORITHM FOR PRIOR / CONCOMITANT / POST-TREATMENT MEDICATIONS

In case of partial or missing medication start and/or stop dates, impute the partial or missing dates using the algorithm below.

If a medication has some missing components in both the start and stop dates, first impute the stop date.

Impute stop date as latest possible date

- If only day unknown, impute to the earlier of (last day of the month; date of SEP380-303 last contact).
- If month and day unknown, impute to the earlier of (31st December; date of SEP380-303 last contact).
- If stop date is completely unknown and medication is not ongoing, impute to date of SEP380-303 last contact.

Impute start date as earliest possible date

CRF questions: 'Started prior to first dose?' = Yes; 'Started after last dose of study medication?' = No.

- If only day unknown, impute to the first day of the month.
- If month and day unknown, impute to the 1st January.
- If start date is completely unknown, impute to the earlier of (date of informed consent*; full or imputed medication stop date [if not missing]).

CRF questions: 'Started prior to first dose?' = No; 'Started after last dose of study medication?' = Yes.

- If only day unknown, impute to the later of (first day of the month; SEP380-303 OLE study med end date + 1).
- If month and day unknown, impute to the later of (1st January; SEP380-303 OLE study med end date + 1).
- If start date is completely unknown, impute to SEP380-303 OLE study med end date + 1.

CRF questions: 'Started prior to first dose?' = No; 'Started after last dose of study medication?' = No.

- If only day unknown, impute to the later of (first day of the month; SEP380-303 OLE study med start date).
- If month and day unknown, impute to the later of (1st January; SEP380-303 OLE study med start date).
- If start date is completely unknown, impute to SEP380-303 OLE study med start date.

Then assign a medication into prior, concomitant, or post-treatment

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

- If medication stop date < SEP380-303 OLE study med start date, assign as prior.
- If (SEP380-303 OLE study med start date ≤ medication stop date ≤ SEP380-303 OLE study med end date) and

    1. medication start date < SEP380-303 OLE study med start date, assign as prior and concomitant.

2. SEP380-303 OLE study med start date ≤ medication start date ≤ SEP380-303 OLE study med end date, assign as concomitant.

- If (medication start date > SEP380-303 OLE study med end date on ongoing) and

1. medication start date < SEP380-303 OLE study med start date, assign as prior, concomitant, and post-treatment.
2. SEP380-303 OLE study med start date ≤ medication start date ≤ SEP380-303 OLE study med end date, assign as concomitant and post-treatment.
3. medication start date > SEP380-303 OLE study med end date, assign as post-treatment.

APPENDIX 3. EQ-5D-5L INDEX VALUE CALCULATION

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value using an appropriate EQ-5D-5L value set. If a standard EQ-5D-5L value set is not available, but an EQ-5D-3L value set is available, a “crosswalk” value set can be used to derive the index value. For multiregional trials, EuroQol recommends applying a single standard value set (or crosswalk value set) to all study sites. For this study, the US EQ-5D-5L standard value set will be used for all countries.

Please refer the following EuroQol website for EQ-5D-5L value sets and further information.

https://euroqol.org/publications/key-euroqol-references/value-sets/

APPENDIX 4. 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

APPENDIX 5. ADVERSE EVENT OF SPECIAL INTEREST (AESI)

During the trial ongoing period and prior to database lock, adverse event customized query defined in this section is used more for AESI reconciliation purposes. Electronic data capture (EDC) system of clinical database contains an AESI tick box, which allow any event term listed below be ticked, thus would encompass any such event in EDC. In that way AESI per customed query (such as hyperprolactinemia-related adverse event) can reconciled for any terms that potentially meet the protocol AESI criteria which have not been identified as such via the AESI tick box (and vice versa). Final definition of each customed query will be finalized right before the DBL and displayed in this SAP before the sign-off. AE preferred terms listed in this section are per MEDDRA version 24.1.

A5.1 Hyperprolactinemia-related AEs (Customized)

"Hyperprolactinemia-related AEs" (customized) is defined as AEs with any of the following preferred terms and all preferred terms that include the word "FRACTURE".

Hyperprolactinemia		
AMENORRHOEA	AMENORRHOEA-GALACTORRHOEA SYNDROME	ANORGASMIA
ANOVULATORY CYCLE	BLOOD OESTROGEN ABNORMAL	BLOOD OESTROGEN DECREASED
BLOOD PROLACTIN ABNORMAL	BLOOD PROLACTIN INCREASED	BONE DEMINERALISATION
BONE DENSITY ABNORMAL	BONE FORMATION TEST ABNORMAL	BONE METABOLISM BIOCHEMICAL MARKER INCREASED
BONE METABOLISM DISORDER	BONE RESORPTION TEST ABNORMAL	BREAST DISCHARGE
BREAST DISCOMFORT	BREAST DISORDER	BREAST DISORDER FEMALE
BREAST DISORDER MALE	BREAST ENGORGEMENT	BREAST ENLARGEMENT
BREAST FIBROSIS	BREAST HYPERPLASIA	BREAST INFLAMMATION
BREAST OEDEMA	BREAST PAIN	BREAST SWELLING
BREAST TENDERNESS	DISTURBANCE IN SEXUAL AROUSAL	EJACULATION DISORDER
ERECTILE DYSFUNCTION	FEMALE ORGASMIC DISORDER	FEMALE SEXUAL AROUSAL DISORDER
FEMALE SEXUAL DYSFUNCTION	FIBROCYSTIC BREAST DISEASE	GALACTOCELE
GALACTORRHOEA	GALACTOSTASIS	GYNAECOMASTIA
HIRSUTISM	HYPERPROLACTINAEMIA	HYPOGONADISM
HYPOMENORRHOEA	INFERTILITY	LIBIDO DECREASED
LIBIDO DISORDER	MACROPROLACTINAEMIA	MALE ORGASMIC DISORDER
MALE SEXUAL DYSFUNCTION	MENSTRUAL DISORDER	MENSTRUATION DELAYED
MENSTRUATION IRREGULAR	METRORRHAGIA	NIPPLE OEDEMA
NIPPLE PAIN	NIPPLE SWELLING	OESTROGEN DEFICIENCY
OESTROGENS TOTAL URINE DECREASED	OLIGOMENORRHOEA	OSTEOPENIA
OSTEOPOROSIS	PAINFUL EJACULATION	PITUITARY AMENORRHOEA
PREMATURE EJACULATION	PROLACTIN-PRODUCING PITUITARY TUMOUR	PSEUDOGYNAECOMASTIA
SEXUAL DYSFUNCTION	SEXUAL INHIBITION	
BREAST ENLARGEMENT FEMALE	HYPOGONADISM FEMALE	HYPOGONADISM MALE
PRIMARY HYPOGONADISM	SECONDARY HYPOGONADISM	INFERTILITY FEMALE
INFERTILITY MALE	LOSS OF LIBIDO	ORGANIC ERECTILE DYSFUNCTION
PSYCHOGENIC ERECTILE DYSFUNCTION		

A5.2 Extrapyramidal Syndrome (EPS) related AEs (Broad)

A "broad" SMQ search includes both the "narrow" scope terms and the additional "broad" scope terms. SMQ "Extrapyramidal syndrome [20000095] (broad)" is defined as AEs with any of the following PTs, which includes all 4 sub-SMQs (Akathisia [20000096], Dyskinesia (including tardive dyskinesia) [20000097], Dystonia [20000098], and Parkinson-like events [20000099])

Akathisia [20000096]		
Narrow		
AKATHISIA		
Broad		
EXTRAPYRAMIDAL DISORDER	HYPERKINESIA	HYPERKINESIA NEONATAL
MOTOR DYSFUNCTION	MOVEMENT DISORDER	PSYCHOMOTOR HYPERACTIVITY
RESTLESSNESS		
Dyskinesia [20000097]		
Narrow		
ATHETOSIS	BALLISMUS	BUCCOGLOSSAL SYNDROME
CHOREA	CHOREOATHETOSIS	DOPAMINE DYSREGULATION SYNDROME
DYSKINESIA	DYSKINESIA NEONATAL	DYSKINESIA OESOPHAGEAL
GRIMACING	OCULOGYRIC CRISIS	PHARYNGEAL DYSKINESIA
PROTRUSION TONGUE	RABBIT SYNDROME	RESPIRATORY DYSKINESIA
TARDIVE DYSKINESIA		
Broad		
ABNORMAL INVOLUNTARY MOVEMENT SCALE	CHRONIC TIC DISORDER	COMPLEX TIC
DROOLING	EXTRAPYRAMIDAL DISORDER	MOTOR DYSFUNCTION
MOVEMENT DISORDER	MUSCLE TWITCHING	PROVISIONAL TIC DISORDER
SECONDARY TIC	TIC	
Dystonia [20000098]		
Narrow		
DYSTONIA	DYSTONIC TREMOR	EMPROSTHOTONUS
MEIGE'S SYNDROME	OCULOGYRIC CRISIS	OPISTHOTONUS
OROMANDIBULAR DYSTONIA	PHARYNGEAL DYSTONIA	PLEUROTHOTONUS
SPASMODIC DYSPHONIA	TORTICOLLIS	TRISMUS
WRITER'S CRAMP		
Broad		
BLEPHAROSPASM	CHRONIC TIC DISORDER	COMPLEX TIC
DROOLING	EXTRAPYRAMIDAL DISORDER	FACIAL SPASM
GAIT INABILITY	LARYNGOSPASM	MOTOR DYSFUNCTION
MOVEMENT DISORDER	MUSCLE CONTRACTIONS INVOLUNTARY	MUSCLE SPASMS
MUSCLE SPASTICITY	MUSCLE TIGHTNESS	MUSCLE TONE DISORDER
MUSCLE TWITCHING	MUSCULOSKELETAL STIFFNESS	OESOPHAGEAL SPASM
OROPHARYNGEAL SPASM	POSTURE ABNORMAL	POSTURING
PROVISIONAL TIC DISORDER	RISUS SARDONICUS	SECONDARY TIC
TIC	TONGUE SPASM	TORTICOLLIS PSYCHOGENIC
UVULAR SPASM		
Parkinson-like events [20000099]		
Narrow		
AKINESIA	BRADYKINESIA	COGWHEEL RIGIDITY
FREEZING PHENOMENON	HYPERTONIA	HYPERTONIA NEONATAL
HYPOKINETIC DYSARTHRIA	MUSCLE RIGIDITY	ON AND OFF PHENOMENON
PARKINSONIAN CRISIS	PARKINSONIAN GAIT	PARKINSONIAN REST TREMOR
PARKINSONISM	PARKINSONISM HYPERPYREXIA SYNDROME	PARKINSON'S DISEASE
PARKINSON'S DISEASE PSYCHOSIS	PROPULSIVE GAIT	RESTING TREMOR
Broad		
ACTION TREMOR	BRADYPHRENIA	DROOLING
DYSPHONIA	EXTRAPYRAMIDAL DISORDER	FINE MOTOR SKILL DYSFUNCTION
GAIT DISTURBANCE	HYPOKINESIA	HYPOKINESIA NEONATAL
LARYNGEAL TREMOR	MICROGRAPHIA	MOBILITY DECREASED
MOTOR DYSFUNCTION	MOVEMENT DISORDER	MUSCLE TONE DISORDER
MUSCULOSKELETAL STIFFNESS	POSTURAL REFLEX IMPAIRMENT	POSTURAL TREMOR
REDUCED FACIAL EXPRESSION	TREMOR	TREMOR NEONATAL
WALKING DISABILITY		

A5.3 Torsade de pointes/QT Prolongation (Broad and Narrow) related AEs

SMQ "Torsade de Pointes/QT prolongation [20000001] (broad and narrow)" is defined as AEs with any of the following PTs:

Torsade de Pointes/QT prolongation [20000001]		
Narrow		
ELECTROCARDIOGRAM QT INTERVAL ABNORMAL	ELECTROCARDIOGRAM QT PROLONGED	LONG QT SYNDROME
LONG QT SYNDROME CONGENITAL	TORSADE DE POINTES	VENTRICULAR TACHYCARDIA
Broad		
ARRHYTHMIC STORM	CARDIAC ARREST	CARDIAC DEATH
CARDIAC FIBRILLATION	CARDIO-RESPIRATORY ARREST	ELECTROCARDIOGRAM REPOLARISATION ABNORMALITY
ELECTROCARDIOGRAM U WAVE INVERSION	ELECTROCARDIOGRAM U WAVE PRESENT	ELECTROCARDIOGRAM U-WAVE ABNORMALITY
LOSS OF CONSCIOUSNESS	SUDDEN CARDIAC DEATH	SUDDEN DEATH
SYNCOPE	VENTRICULAR ARRHYTHMIA	VENTRICULAR FIBRILLATION
VENTRICULAR FLUTTER	VENTRICULAR TACHYARRHYTHMIA	

APPENDIX 6. PREDEFINED POTENTIALLY CLINICALLY SIGNIFICANT (PCS) CRITERIA FOR LABORATORY VALUES

Parameter	PCS Range (SI units)	PCS Range (CV units)
Serium Chemistry		
Sodium	< 130 mmol/L	< 130 mEq/L
	> 150 mmol/L	> 150 mEq/L
Potassium	< 3 mmol/L	< 3 mEq/L
	> 5.5 mmol/L	> 5.5 mEq/L
Chloride	≤ 90 mmol/L	≤ 90 mEq/L
	≥ 118 mmol/L	≥ 118 mEq/L

Parameter	PCS Range (SI units)	PCS Range (CV units)
Calcium	< 1.75 mmol/L	< 7.01 mg/dL
	≥ 3.1 mmol/L	≥ 12.42 mg/dL
Phosphate	< 0.65 mmol/L	< 2.01 mg/dL
	> 1.65 mmol/L	> 5.11 mg/dL
Bicarbonate	< 15.1 mmol/L	< 15.1 mEq/L
	> 34.9 mmol/L	> 34.9 mEq/L
Magnesium	< 0.4 mmol/L	< 0.97 mg/dL
	> 1.23 mmol/L	> 2.99 mg/dL
AST	≥ 3 x ULN	≥ 3 x ULN
ALT	≥ 3 x ULN	≥ 3 x ULN
Alkaline Phosphatase	≥ 1.5 x ULN	≥ 1.5 x ULN
GGT (Gamma-Glutamyl Transferase)	≥ 2.5 x ULN	≥ 2.5 x ULN
LDH	≥ 3 x ULN	≥3 x ULN
Creatine Kinase	≥ 3 x ULN	≥ 3 x ULN
Creatinine	≥ 177 umol/L	≥ 2.0 mg/dL
Creatinine Clearance	< 0.48343 mL/s	< 28.95 mL/min
BUN	≥ 10.7 mmol/L	≥ 29.96 mg/dL
Total Bilirubin	>= 34.2 umol/L OR > 2 x ULN	>= 2.0 mg/dL OR > 2 x ULN
Total protein	≤ 45 g/L	≤ 4.5 g/dL
	≥ 100 g/L	≥ 10 g/dL
Albumin	≤ 25 g/L	≤ 2.5 g/dL
Total Cholesterol (fasting)	≥ 7.76 mmol/L	≥ 300 mg/dL
HDL-Cholesterol (fasting)	< 0.78 mmol/L	< 30 mg/dL
LDL Cholesterol (fasting)	> 4.14 mmol/L	> 160 mg/dL
Triglycerides (fasting)	> 3.42 mmol/L	> 302.92 mg/dL
Uric acid Male Female	 > 595 umol/L > 476 umol/L	 > 10 mg/dL > 8 mg/dL
Glucose (fasting)	< 2.78 mmol/L	< 50.09 mg/dL
	> 13.9 mmol/L	> 150.45 mg/dL
HbA1c	≥ 0.075	≥ 7.5%
Prolactin	≥ 5 x ULN	≥ 5 x ULN
Hematology		
WBC	≤ 2.8 x10 ^{9}/L	≤ 2.8 x10 ^{3}/µL
	≥ 16 x10 ^{9}/L	≥ 16 x10 ^{3}/µL
Neutrophils (abs)	< 0.5 x 10^9/L	< 0.5 x 10^3/µL
	> 13.5 x 10^9/L	> 13.5 x 10^3/µL
Lymphocytes (abs)	> 12 x 10^9/L	> 12 x 10^3/µL
Monocytes (abs)	> 2.5 x 10^9/L	> 2.5 x 10^3/µL
Eosinophils (abs)	> 1.6 x 10^9/L	> 1.6 x 10^3/µL

Parameter	PCS Range (SI units)	PCS Range (CV units)
Basophils (abs)	> 1.6 x 10^9/L	> 1.6 x 10^3/µL
Neutrophils (relative)	≤ 0.15	≤ 15%
	> 0.85	> 85%
Lymphocytes (relative)	≥ 0.75	≥ 75%
Monocytes (relative)	≥ 0.15	≥ 15%
Eosinophils (relative)	≥ 0.10	≥ 10%
Basophils (relative)	≥ 0.10	≥ 10%
Hemoglobin	Male: ≤ 115 g/L	Male: ≤ 11.5 g/dL
	Female: ≤ 95 g/L	Female: ≤ 9.5 g/dL
	Male: ≥ 190 g/L	Male: ≥ 19.0 g/dL
	Female: ≥175 g/L	Female: ≥ 17.5 g/dL
Hematocrit	Male: ≤ 0.37	Male: ≤ 37%
	Female: ≤ 0.32	Female: ≤ 32%
	Male: ≥ 0.60	Male: ≥ 60%
	Female: ≥ 0.54	Female: ≥ 54%
RBC	≤ 3.5 x 10^{12}/L	≤ 3.5 x 10^6/µL
	≥ 6.4 x 10^{12}/L	≥ 6.4 x 10^6/µL
Platelet Count	≤ 75 x 10^9/L	≤ 75 x 10^3/µL
	≥ 700 x 10^9/L	≥ 700 x 10^3/µL
Coagulation		
aPTT (sec)	> 1.5 x ULN	> 1.5 x ULN
INR (ratio)	> 1.5 x ULN	> 1.5 x ULN
Urinalysis		
RBC	>25 hpf	25 hpf
WBC	>25 hpf	25 hpf

APPENDIX 7. SCHEDULE OF EVENTS

		12-Month Open-Label Treatment Period							
Study Visit Number[a]	**V1E**	**V2E**	**V3E**	**V4E**	**V5E**	**V6E**	**V7E**	**V8E**	**V9E**
Study Week or Month	**Baseline**[b]	**Week 2**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**
Study Day	**-1**	**14 (± 2)**	**30 (± 2)**	**60 (± 5)**	**90 (± 5)**	**120 (± 5)**	**150 (± 5)**	**180 (± 5)**	**210 (± 5)**
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Dispense Study Drug	X	X	X	X	X	X	X	X	X
Study Drug Accountability		X	X	X	X	X	X	X	X
Demographics	X								
Physical Examination	Core							X	
Neurological Examination	Core							X	
Prior/Concomitant Medications[c]	X	X	X	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	X	X	X	X
Schedule Telephone Check-in With Subject[d]	X	X	X	X	X	X	X	X	X
SAFETY ASSESSMENTS									
Vital Sign Measurements	Core	X	X	X	X	X	X	X	X
Weight	Core	X	X	X	X	X	X	X	X
Waist Circumference	Core							X	
Adverse Events[e]	X	X	X	X	X	X	X	X	X
12-Lead ECG[f]	Core	X	X	X	X	X	X	X	X
Serum Chemistry[g]	Core	X		X		X		X	
Hematology	Core	X		X		X		X	
Urinalysis	Core	X		X		X		X	
Serum Prolactin[h]	Core	X		X		X		X	
Blood Sampling for Plasma PK and Plasma Prolactin[i]	Core	X		X		X		X	

		12-Month Open-Label Treatment Period							
Study Visit Number[a]	**V1E**	**V2E**	**V3E**	**V4E**	**V5E**	**V6E**	**V7E**	**V8E**	**V9E**
Study Week or Month	**Baseline**[b]	**Week 2**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**
Study Day	**-1**	**14 (± 2)**	**30 (± 2)**	**60 (± 5)**	**90 (± 5)**	**120 (± 5)**	**150 (± 5)**	**180 (± 5)**	**210 (± 5)**
Hemoglobin A1c (HbA1c)	Core			X		X		X	
Lipid Panel[g]	Core			X		X		X	
Serum Insulin[g]	Core			X		X		X	
High-sensitivity C-Reactive Protein (hs-CRP)	Core							X	
Thyroid Panel	Core			X		X		X	
Urine Pregnancy Test (females of childbearing potential)[j]	Core		X	X	X	X	X	X	X
Rapid Urine Drug Test	Core	X	X	X	X	X	X	X	X
Young Mania Rating Scale (YMRS)	Core	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	Core	X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)	Core	X		X		X		X	
Barnes Akathisia Scale (BARS)	Core	X		X		X		X	
Modified Simpson-Angus Scale (SAS)	Core	X		X		X		X	
Physician's Withdrawal Checklist (PWC)									

		12-Month Open-Label Treatment Period							
Study Visit Number[a]	**V1E**	**V2E**	**V3E**	**V4E**	**V5E**	**V6E**	**V7E**	**V8E**	**V9E**
Study Week or Month	**Baseline** [b]	**Week 2**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**
Study Day	**-1**	**14 (± 2)**	**30 (± 2)**	**60 (± 5)**	**90 (± 5)**	**120 (± 5)**	**150 (± 5)**	**180 (± 5)**	**210 (± 5)**
EFFECTIVENESS ASSESSMENTS									
Montgomery-Asberg Depression Rating Scale (MADRS)	Core	X	X	X	X	X	X	X	X
Clinical Global Impression-Bipolar Version-Severity of Illness (CGI-BP-S)	Core	X	X	X	X	X	X	X	X
Hamilton Anxiety Rating Scale (HAM-A)	Core			X		X		X	
Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16)	Core			X		X		X	
Sheehan Disability Scale (SDS)	Core			X		X		X	
EuroQoL - 5 Dimension - 5 Level (EQ-5D-5L)	Core			X		X		X	
Snaith-Hamilton Pleasure Scale (SHAPS)	Core			X		X		X	

	12-Month Open-Label Treatment Period					Follow-Up
Study Visit Number[a]	**V10E**	**V11E**	**V12E**	**V13E**	**V14E (EOT/ET)**	**V15E**[m]
Study Week or Month	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**[k,l] **(Week 52)**	**7 (± 2) days after last dose**
Study Day	**240 (± 5)**	**270 (± 5)**	**300 (± 5)**	**330 (± 5)**	**360 (+ 5)**	
Informed Consent						
Inclusion/Exclusion Criteria						
Dispense Study Drug	X	X	X	X		
Study Drug Accountability	X	X	X	X	X	
Physical Examination					X	
Neurological Examination					X	
Prior/Concomitant Medications	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	
Schedule Telephone Check-in With Subject[d]	X	X	X	X		
SAFETY ASSESSMENTS						
Vital Sign Measurements	X	X	X	X	X	X
Weight	X	X	X	X	X	
Waist Circumference					X	
Adverse Events	X	X	X	X	X	X
12-Lead ECG	X	X	X	X	X	X
Serum Chemistry[g]	X		X		X	
Hematology	X		X		X	
Urinalysis	X		X		X	
Serum Prolactin[h]	X		X		X	X
Blood Sampling for Plasma PK and Plasma Prolactin[h,i]	X		X		X	X
Hemoglobin A1c (HbA1c)	X		X		X	
Lipid Panel[g]	X		X		X	
Serum Insulin[g]	X		X		X	
High-sensitivity C-Reactive Protein (hs-CRP)					X	

	12-Month Open-Label Treatment Period					Follow-Up
Study Visit Number[a]	**V10E**	**V11E**	**V12E**	**V13E**	**V14E (EOT/ET)**	**V15E**[m]
Study Week or Month	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**[k,l] **(Week 52)**	**7 (± 2) days after last dose**
Study Day	**240 (± 5)**	**270 (± 5)**	**300 (± 5)**	**330 (± 5)**	**360 (+ 5)**	
Urine Pregnancy Test (females of childbearing potential)[j]	X	X	X	X	X	X
Rapid Urine Drug Test	X	X	X	X	X	X
Young Mania Rating Scale (YMRS)	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)	X		X		X	
Barnes Akathisia Scale (BARS)	X		X		X	
Modified Simpson-Angus Scale (SAS)	X		X		X	
Physician's Withdrawal Checklist (PWC)					X	X
EFFECTIVENESS ASSESSMENTS						
Montgomery-Asberg Depression Rating Scale (MADRS)	X	X	X	X	X	
Clinical Global Impression-Bipolar Version-Severity of Illness (CGI-BP-S)	X	X	X	X	X	
Hamilton Anxiety Rating Scale (HAM-A)	X		X		X	
Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16)	X		X		X	
Sheehan Disability Scale (SDS)	X		X		X	
EuroQoL - 5 Dimension - 5 Level (EQ-5D-5L)	X		X		X	
Snaith-Hamilton Pleasure Scale (SHAPS)	X		X		X	

Abbreviations: BL = Baseline; eCRF = electronic case report form; E = extension; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; PK = pharmacokinetic

Note: To ensure subject safety and data integrity, should circumstances warrant and with Sponsor approval, remote site/subject visits may be conducted. There is an extra visit for Japan (Visit 1EJ) on Day 1 that evaluates ECG.

[a] Visit windows are as follows: ± 2 days for Visits 2E (Week 2/Day 14) and 3E (Month 1), ± 5 days for monthly visits between Visit 4E (Month 2) and Visit 13E (Month 11), + 5 days for Visit 14E (Month 12), and ± 2 days for the Follow-up Visit (Visit 15E).
[b] Visit 6/ End of Treatment (EOT) (Day 42) of the lead-in study of SEP-4199 CR serves as the Baseline visit (Day -1) for the present study. "Core" indicates assessments that were conducted at Visit 6/EOT (Day 42) in the lead-in study of SEP-4199 CR and do not need to be repeated for this study.
[c] Medications taken during the lead-in study of SEP-4199 CR that are ongoing at the start of the current extension study will be entered into the eCRF.
[d] Between study visits, subjects will be contacted weekly by telephone.
[e] Adverse events with onset during the lead-in study of SEP-4199 CR and ongoing at the start of the current extension study will be entered into the eCRF.
[f] ECG machine measurements are to be considered for subject eligibility at Baseline.
[g] Subjects are required to fast for at least 8 hours prior to sample collection for laboratory testing.
[h] Prolactin values at open-label Baseline visit (including any repeat testing) will be masked. Prolactin values after the first dose of study drug in the extension study will not be masked.
[i] Blood sample for SEP-4199 population pharmacokinetic analysis for R- and S-enantiomers and/or plasma prolactin measurement will be collected at Visit 2E (Week 2/Day 14), Visit 4E (Month 2), Visit 6E (Month 4), Visit 8E (Month 6), Visit 10E (Month 8), V12E (Month 10), Visit 14E (Month 12), and Follow-up (Visit 15E, 7 ± 2 days after last dose), with a record of the time of last 3 administered doses on the CRF for PK sampling visits during the treatment period. The blood sample will be collected at time of clinical safety laboratory test sample collection. Plasma concentrations of aramisulpride and esamisulpride and plasma prolactin levels will be measured. Remaining plasma from samples may also be used for the additional bioanalytical method development and/or characterization of putative metabolites of amisulpride and for other exploratory measurements, if needed.
[j] Any positive urine β-Human chorionic gonadotropin (hCG) test should be confirmed by a serum β-hCG test.
[k] Visit 14E (Month 12) is the End of Treatment/Early Termination visit. Subjects who discontinue the study prior to Visit 14E will have all Visit 14E procedures performed at the time of discontinuation.
[l] For subjects completing the 12-month treatment period, a visit window of + 5 days is strongly preferred.
[m] Follow-up visit to be scheduled 7 (± 2) days after last dose of study drug.