SEP-4199 CR

Clinical Study Protocol 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)

IND No. 138,026

EudraCT No. 2021-002108-11

Version 2.02

Incorporates Non-substantial Amendment 2.00

Incorporates Non-substantial Amendment 1.00

06 December 2022

[redacted]

RESTRICTED DISTRIBUTION OF PROTOCOLS

This document contains information confidential and/or of proprietary interest to Sumitomo Pharma Co., Ltd. (SMP) and/or Sunovion Pharmaceuticals Inc. (including their predecessors, subsidiaries, or affiliates). The information cannot be disclosed to any third party or used for any purpose other than the purpose for which it is being submitted without the prior written consent of the appropriate Sumitomo Pharma company.

This information is being provided to you for the purpose of conducting a clinical study for Sunovion Pharmaceuticals Inc. You may disclose the contents of this protocol to the study personnel under your supervision and to your Institutional Review Board or Independent Ethics Committee for the above purpose. You may not disclose the contents of this protocol to any other parties, unless such disclosure is required by government regulations or laws, without the prior written permission of Sunovion Pharmaceuticals Inc.

Any data gathered during the conduct of this protocol and supplemental information (eg, a protocol amendment) that may be added to this document is also proprietary to Sunovion Pharmaceuticals Inc. and should be handled consistently with that stated above.

EMERGENCY CONTACTS

Table 1: Emergency Contact Information

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.; Sponsor in Japan: Sumitomo Pharma Co., Ltd. (SMP)

Name of Investigational Product: SEP-4199 CR

Name of Active Ingredient: aramisulpride (85%), esamisulpride (15%)

Proposed Indication: Major depressive episode associated with bipolar I disorder (bipolar I depression)

Title of Study: 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)

Study Centers: Up to 90 sites in Europe (EUR), Japan (JP), North America, and Latin America that have completed a 6-week double-blind placebo-controlled lead-in study of SEP-4199 CR (hereinafter referred to as lead-in study of SEP-4199 CR)

Phase of Development: 3

Study Objectives:

To evaluate the long-term safety, tolerability, and effectiveness of SEP-4199 CR formulation at a flexible daily dose of 200 mg/day or 400 mg/day in subjects who previously completed a lead-in study of SEP-4199 CR for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression).

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).

Additional 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).

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).

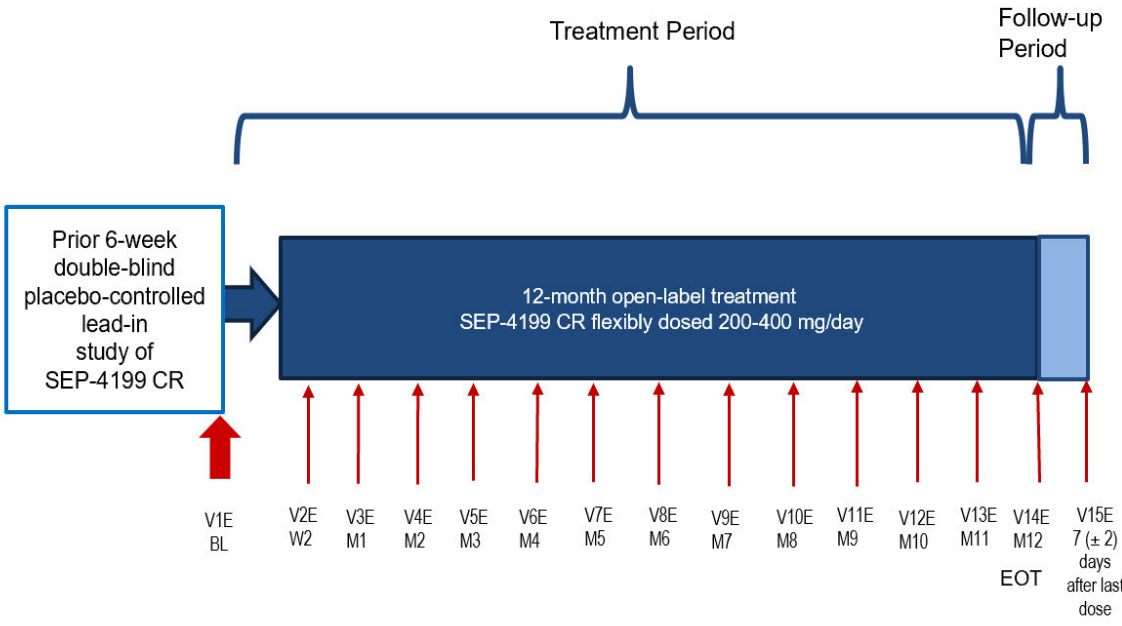
Pharmacokinetics and Pharmacodynamics Objectives:

- 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.

Study Design: 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.

Study Schematic



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

Baseline (Visit 1E; Day -1)

Visit 6/End of Treatment (EOT) (Day 42) of the lead-in study of SEP-4199 CR will serve as the Baseline visit of the current open-label extension study. Subjects who completed 6 weeks of double-blind treatment in a lead-in study of SEP-4199 CR and who meet eligibility criteria to continue into the current extension study may be enrolled. Baseline values for safety and effectiveness measures for this study will be carried over from Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR for each subject. Subjects should continue dosing with SEP-4199 CR in the current open-label study without dosing interruption.

Open-Label Treatment Period (Day 1 to Visit 14E/Month 12)

Subjects will self-administer the study drug on an outpatient basis once daily beginning on Day 1 and continue for 12 months. Subjects will be instructed to administer study drug as a single oral dose in the morning at approximately the same time each day. The last dose of study drug will be self-administered by the subject at home on the morning of Visit 14E (Month 12).

During the open-label treatment period, subjects will have clinic visits at Week 2/Day 14 and Months 1 to 12. In order to facilitate scheduling of clinic visits and telephone calls, a window of ± 2 days will be allowed for Visits 2E (Week 2/Day 14) and 3E (Month 1); a window of ± 5 days will be allowed for Visits 4E (Month 2) to 13E (Month 11), and a window of +5 days will be allowed for Visit 14E (Month 12). Between study visits, subjects will be contacted weekly by telephone.

All subjects will initiate treatment with SEP-4199 CR 200 mg/day. The dose may be increased to 400 mg/day at Visit 2E (Week 2/Day 14) or later, based on the Investigator's judgment. However, if clinically indicated, the dose may be increased as early as Day 7 at an unscheduled visit. The dose may be decreased to 200 mg/day at any time thereafter for tolerability. If a dose decrease is needed between study visits, subjects will return to the clinic for an unscheduled visit for drug dispensation. Dose increases will occur only at scheduled or unscheduled clinic visits. Prior to a dose increase, safety assessments will be completed, including but not limited to evaluation of AEs, concomitant medications, vital signs, and ECGs. Subjects whose ECG results, based on machine reading, show increase from Baseline in QT interval corrected for heart rate using Fridericia's formula (QTcF) interval ≥ 30 milliseconds (msec) or whose QTcF interval is ≥ 480 msec at the 200 mg/day dose are not allowed to have their dose increased to 400 mg/day. Subjects with hyperprolactinemia-related AESI are not allowed to have the dose increased to 400 mg/day.

End of Treatment (EOT)/Early Termination (ET) (Visit 14E: Month 12)

Subjects will have Visit 14E at Month 12 (+ 5 days) for EOT assessments of safety and effectiveness.

Subjects who prematurely discontinue from the study will undergo an ET visit to include all Visit 14E assessments and procedures.

Follow-up Period (Visit 15E, 7 [± 2] days after last dose)

All subjects will have a follow-up visit for safety and tolerability assessments 7 (± 2) days after their last dose of study drug. Assessment of potential withdrawal effects will also be made during the follow-up period.

Safety Assessments

Safety and tolerability will be monitored throughout the study by physical and neurological examinations, vital signs, AE monitoring, ECGs, and clinical laboratory tests. Body weight, body mass index (BMI), and waist circumference will also be recorded. AESI will include, but are not limited to, hyperprolactinemia-related AEs. AEs associated with extrapyramidal symptoms (EPS) will be summarized; and movement disorders and akathisia will be assessed by AIMS, BARS, and the modified SAS. Manic symptoms will be monitored using the YMRS. Suicidality will be monitored using the C-SSRS. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves; in addition, an associated AE must be

reported. Potential withdrawal effects will be assessed using the PWC. A Data and Safety Monitoring Board (DSMB) will review safety data at regular intervals during the study. Details of these safety assessments are provided in Section 11.4 and Table 2.

Effectiveness Assessments

Effectiveness will be evaluated for depression symptoms using the clinician-rated MADRS, CGI-BP-S Depression scale, and the QIDS-SR16. Anxiety symptoms will be evaluated using the HAM-A. Functional disability will be assessed using the SDS. Quality of life will be assessed using the EQ-5D-5L. Anhedonia symptoms will be evaluated using the SHAPS. Details of these effectiveness assessments are provided in Section 11.3 and in Table 2.

Pharmacokinetic Assessments

Blood samples will be collected for population pharmacokinetics and plasma prolactin at the following visits: 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).

Prior to PK blood sample collection, subjects will record the date and time of their 3 most-recent study drug doses; the clinical site staff will record the dates and times of the 3 doses in the eCRF for each of the PK collection visits during the treatment period.

Plasma samples will be analyzed for concentrations of aramisulpride and esamisulpride using a validated enantioselective liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Plasma samples will also be analyzed for prolactin concentrations by an enzyme-linked immunosorbent assay (ELISA).

Remaining plasma samples after amisulpride PK and prolactin analysis 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.

Number of Subjects (planned): Approximately 355

Diagnosis and Criteria for Subject Inclusion:

Inclusion Criteria:

1. Subject provides written informed consent and is willing and able to comply with the protocol in the opinion of the Investigator.
2. Subject has completed 6 weeks of double-blind treatment and all scheduled assessments from Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR.
3. Subject is medically appropriate for long-term open-label treatment with SEP-4199 CR in the opinion of the Investigator.
4. Female subjects of childbearing potential must agree to use effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken. In the Investigator's judgment, the subject will adhere to this requirement. Contraception requirements are detailed in Section 10.4.
5. Male subjects agree to avoid fathering a child and to use effective methods of birth control throughout the study and until at least 90 days after the last study drug administration. Contraception requirements are detailed in Section 10.4.

Exclusion Criteria:

1. Subject is at high risk of non-compliance in the opinion of the Investigator.
2. Subject plans to initiate treatment with a prohibited psychotropic medication during the study.

3. Subject plans to initiate treatment with transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), or deep brain stimulation (DBS) during the study.
4. Subject experienced a moderate or severe hyperprolactinemia-related AESI in the lead-in study of SEP-4199 CR.
5. Subject will require treatment with a drug that is associated with increases in QTc interval (see Section 23, Appendix IV for a list of medications, not all inclusive).
6. Subject had any of the following at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR based on machine reading:
   - increase in QTcF interval of ≥ 30 msec from Baseline of the lead-in study of SEP-4199 CR AND a QTcF interval ≥ 480 msec
   - increase in QTcF interval ≥ 60 msec from Baseline of the lead-in study of SEP-4199 CR
   - QTcF interval > 500 msec
   - treatment-emergent clinically significant ECG abnormality.
7. Subject is considered by the Investigator to be at imminent risk of suicide or injury to self or others, has a MADRS item 10 (suicidal ideation) score ≥ 4, or answers "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR.
8. Female subject of childbearing potential has a positive urine pregnancy test at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR or plans to become pregnant during the current study.
9. Subject tests positive for any drug of abuse or cannabis at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR.

Investigational Product, Dosage and Mode of Administration:

SEP-4199 CR will be supplied as 200 mg film-coated tablets and containing a fixed 85:15 ratio of aramisulpride:esamisulpride.

- For the SEP-4199 CR 200 mg/day dose, study drug will consist of 1 x 200 mg tablet.
- For the SEP-4199 CR 400 mg/day dose, study drug will consist of 2 x 200 mg tablets.

Study drug tablets will be self-administered by the subject orally once daily in the morning at approximately the same time each day beginning on Day 1.

Duration of Treatment:

Open-label treatment will be self-administered by the subject once daily for 12 months.

Reference Therapy, Dosage and Mode of Administration:

Not applicable.

Prior and Concomitant Medications:

Any medication, vaccination, or non-pharmacological therapy that is taken by or administered to the subject between the signing of informed consent and final visit or discontinuation will be recorded in the electronic case report form (eCRF).

Concomitant medications in the lead-in study of SEP-4199 CR that were ongoing at Visit 6/EOT (Day 42) will be entered into the eCRF for this study (SEP380-303). All changes in concomitant medications or new medications administered during the study up to the Follow-up Visit (Visit 15E, 7 ± 2 days after last dose) will be recorded.

Treatment with other psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) is prohibited except as noted below.

Ongoing treatment or initiation of treatment with non-pharmacologic psychotherapy is allowed.

Non-psychotropic medications may be used to treat mild, chronic medical conditions. β-adrenergic antagonists used to treat stable hypertension may be continued. In addition, non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol, ibuprofen) are allowed during the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study medication.

Medications for the short-term (no more than 10 days) treatment of an acute medical condition are allowed provided that the medications do not prolong the QTc interval. Section 23, Appendix IV provides a representative, but not exhaustive, list of medications that prolong the QT interval and are not allowed during the study. Routine vaccines (ie, seasonal influenza, pneumonia, COVID-19, etc.) are allowed based on Investigator judgement.

Medications for treatment of movement disorders may be administered if symptoms emerge. Benztropine (≤ 6 mg/day), biperiden (≤ 16 mg/day), trihexyphenidyl (≤ 15 mg/day), or diphenhydramine (≤ 100 mg/day) are permitted as needed to treat extrapyramidal symptoms. Propranolol (≤ 120 mg/day) or amantadine (≤ 300 mg/day) are permitted as needed to treat akathisia.

Concomitant use of anxiolytics, sedatives, and hypnotics is permitted with the following restrictions: Lorazepam is permitted up to 2 mg/day for intolerable anxiety/agitation. Lorazepam (≤ 2 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zolpidem (≤ 10 mg/day), zolpidem CR (≤ 12.5 mg/day), and temazepam (≤ 30 mg/day) may be administered at bedtime for insomnia, as needed. Hypnotic agents should be administered no more than once nightly and should not be used in combination.

In regions that do not have the above specified medications available, similar medications at equivalent dosages may be permitted after consultation with and approval by the Medical Monitor.

Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor.

The use of herbal supplements or other complementary or alternative medications during the trial is not permitted. Further details are provided in Section 10.3.

Study Endpoints:

Safety Endpoints:

- The incidence of overall AEs, discontinuation due to AEs, and SAEs
- The incidence of AESI including but not limited to hyperprolactinemia-related AEs
- Clinical laboratory evaluations (chemistry, hematology, 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 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

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 VAS and Index scores
- Changes in the SHAPS total score

Pharmacokinetic and Pharmacodynamic Endpoints:

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

Statistical Methods:

The safety population will include all subjects who receive at least one dose of study medication. The follow-up population includes all subjects who receive at least one dose of study medication and have at least 1 assessment after the last study drug administration for any evaluation.

A total of 4 analysis groups will be formed based on a subject's previous participation in the lead-in study of SEP-4199 CR (previously randomized to SEP-4199 CR 200 mg/day, previously randomized to SEP-4199 CR 400 mg/day, previously randomized to any SEP-4199 CR dose group, previously randomized to placebo). A group that combines all of these analysis groups will also be presented. Summary tables, wherever applicable, will be presented by analysis group. Where changes are reported, the reference will be to the pretreatment Baseline from the lead-in study of SEP-4199 CR and indicated as "Double-blind (DB) Baseline". Where relevant, changes from Baseline for the open-label study, defined as the Week 6 assessment in the double-blind study or the last assessment prior to the first dose of study medication in the open-label study, will also be reported, and will be referred to as the open-label study Baseline or "OL Baseline". Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, first quartile [Q1], third quartile [Q3], range, 95% confidence interval [CI] as needed) and categorical variables will be reported as frequencies and percentages at DB Baseline, OL Baseline, each of post-OL visit, and endpoint. No statistical comparisons will be conducted and no inferential statistics on effectiveness and safety will be presented.

The safety data will be summarized by analysis group based on the safety population. In addition, for a few selected safety assessments (ie, AE, ECG, laboratory results, and vital signs), descriptive summary by analysis group will be provided based on the follow-up population, separately.

A treatment-emergent adverse event (TEAE) is an adverse event with onset data on or after the first day of the open-label treatment period through 7 days after study drug discontinuation (14 days for serious adverse events). The start of the open-label treatment period is defined as the first dose day for subjects previously randomized to placebo group and the OL Baseline visit date for subjects previously randomized to SEP-4199 CR groups.

The incidence of AEs, SAEs, and AEs leading to discontinuation due to AEs (or SAEs) will be summarized by analysis group (by presenting the number and percentage of subjects with one or more

AEs in each category). The number and proportion of subjects with one or more AEs within a system organ class (SOC) and by preferred term will be presented by analysis group as well. The incidence of AEs of special interest, including but not limited to hyperprolactinemia related AEs, will be summarized for overall and by gender, as appropriate. Incidence of post-treatment adverse events (defined as an AE with a start date after the date of last dose of study drug through the last contact/visit in the follow-up period) will be summarized separately for subjects in the follow-up population.

For safety assessments, descriptive statistics will be provided for observed values and changes from DB Baseline and OL Baseline, respectively, by study visit and analysis group for the continuous variables. Frequencies and percentages will be reported for categorical variables by study visit and analysis group. The markedly abnormal values for selected safety parameters will be summarized, as appropriate.

The number and percentage of subjects with suicidal ideation and/or suicidal behavior, emergence or worsening of suicidal ideation or suicidal behavior will be summarized by analysis group for the open-label treatment period.

The PWC score will be summarized by presenting descriptive statistics of observed values and changes from Week 52/EOT by analysis group based on the follow-up population.

Descriptive statistics of observed values and changes from DB Baseline and OL Baseline will be summarized by study visit and analysis group for effectiveness parameters (continuous). At a visit in the extension study, responders relative to DB Baseline are defined as those who show a 50% or more reduction (ie, improvement) from DB Baseline in MADRS total score. At a post-OL Baseline visit, responders relative to OL Baseline are defined as those who show a 50% or more reduction (ie, improvement) from OL Baseline. Remitters at any visit are defined as subjects with a MADRS total score of ≤ 12. Frequencies and percentages of MADRS responders relative to both DB Baseline and OL Baseline, and frequencies and percentages of remitters will be summarized over time by analysis group.

Sample Size Consideration: Assuming a completion rate of 85% in the lead-in study of SEP-4199 CR and an 80% rollover rate of completers from that study to the current extension study, it is estimated that approximately 355 subjects will be enrolled.

Table 2: Schedule of Assessments

		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								
Informed Consent for Duplicate Subject Check (where local regulations allow)	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 and Body Mass Index[e]	Core	X	X	X	X	X	X	X	X
Waist Circumference	Core							X	
Adverse Events[f]	X	X	X	X	X	X	X	X	X
12-Lead ECG[g]	Core	X	X	X	X	X	X	X	X
Serum Chemistry[h]	Core	X		X		X		X	

Table 2: Schedule of Assessments (Continued)

		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)**
Hematology	Core	X		X		X		X	
Urinalysis	Core	X		X		X		X	
Serum Prolactin[i]	Core	X		X		X		X	
Blood Sampling for Plasma PK and Plasma Prolactin[j]	Core	X		X		X		X	
Hemoglobin A1c (HbA1c)	Core			X		X		X	
Lipid Panel[h]	Core			X		X		X	
Serum Insulin[h]	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)[k,l]	Core		X	X	X	X	X	X	X
Rapid Urine Drug Test[l]	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	

Table 2: Schedule of Assessments (Continued)

		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)**
Physician's Withdrawal Checklist (PWC)									
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	

Table 2: Schedule of Assessments (Continued)

	12-Month Open-Label Treatment Period					Follow-Up
Study Visit Number[a]	**V10E**	**V11E**	**V12E**	**V13E**	**V14E (EOT/ET)**	**V15E**[o]
Study Week or Month	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**[m,n] **(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 and Body Mass Index[e]	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[h]	X		X		X	
Hematology	X		X		X	
Urinalysis	X		X		X	
Serum Prolactin[i]	X		X		X	X
Blood Sampling for Plasma PK and Plasma Prolactin[i,j]	X		X		X	X
Hemoglobin A1c (HbA1c)	X		X		X	
Lipid Panel[h]	X		X		X	
Serum Insulin[h]	X		X		X	
High-sensitivity C-Reactive Protein (hs-CRP)					X	

Table 2: Schedule of Assessments (Continued)

	12-Month Open-Label Treatment Period					Follow-Up
Study Visit Number[a]	**V10E**	**V11E**	**V12E**	**V13E**	**V14E (EOT/ET)**	**V15E**[o]
Study Week or Month	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**[m,n] **(Week 52)**	**7 (± 2) days after last dose**
Study Day	**240 (± 5)**	**270 (± 5)**	**300 (± 5)**	**330 (± 5)**	**360 (+ 5)**	
Thyroid Panel	X		X		X	
Urine Pregnancy Test (females of childbearing potential)[k,l]	X	X	X	X	X	X
Rapid Urine Drug Test[l]	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; hCG = human chorionic gonadotropin; PK = pharmacokinetic

Note: To ensure subject safety and data integrity, should circumstances warrant and with Sponsor approval, remote site/subject visits may be conducted.

[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] BMI does not need to be calculated by the clinical site staff as it will be calculated in the analysis.

[f] 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.

[g] ECG machine measurements are to be considered for subject eligibility at Baseline.

[h] Subjects are required to fast for at least 8 hours prior to sample collection for laboratory testing at Visit 2E, Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E (EOT/ET); fasting is also required at Week 6 (EOT) in the lead-in study of SEP-4199 CR, which serves as baseline (Visit 1E) in this long-term safety study.

[i] 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.

[j] 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 eCRF 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.

[k] For females of childbearing potential, any positive urine β- hCG test should be confirmed by a serum β-hCG test.

[l] Unscheduled urine pregnancy (females of childbearing potential) and urine drug tests may be administered based on Investigator discretion. Point of care (POC) testing will be used for the urine pregnancy test and the rapid urine drug test. A urine drug screen should be submitted to the central lab for any positive rapid urine drug test throughout the study. Positive results for any of these assessments should be discussed with the Medical Monitor.

[m] 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.

[n] For subjects completing the 12-month treatment period, a visit window of + 5 days is strongly preferred.

[o] Follow-up visit to be scheduled 7 (± 2) days after last dose of study drug.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CFR	Code of Federal Regulations
CGI-BP-S	Clinical Global Impression – Bipolar Version-Severity of Illness
CI	Confidence interval
C_{max}	Maximum concentration of drug
COVID-19	Coronavirus disease 2019
CR	Controlled release
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	Double-blind
DBP	Diastolic blood pressure
DBS	Deep brain stimulation
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
E	Extension
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
EDC	Electronic Data Capture
EOT	End of treatment
EPS	Extrapyramidal symptoms
EQ-5D-5L	EuroQoL - 5 Dimension – 5 Level
EQ-VAS	EuroQol Visual Analogue Scale
ET	Early termination

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
EU or EUR	European Union / Europe
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HAM-A	Hamilton Anxiety Rating Scale
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HR	Heart rate
Hs-CRP	High-sensitivity C-Reactive Protein
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IR	Immediate release
IRB	Institutional Review Board
ITT	Intention-to-treat
IXRS	Interactive Web Response System
M	Month
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
OL	Open-label
PCS	Potentially clinically significant
PD	Pharmacodynamics
PET	Positron emission tomography
PK	Pharmacokinetic(s)
POC	Point of care
Pop-PK	Population pharmacokinetics
PR	Time between P wave and QRS in electrocardiography
PRN	As needed
PT	Preferred term
PVG	Pharmacovigilance

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
PWC	Physician's Withdrawal Checklist
Q1	First quartile (25th percentile)
Q3	Third quartile (75th percentile)
QIDS-SR16	Quick Inventory of Depressive Symptomatology – Self-Report
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	RR interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SBP	Systolic blood pressure
SDS	Sheehan Disability Scale
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-A	Structured Interview Guide for the HAM-A
SOC	System organ class
SOPs	Standard operating procedures
TEAE	Treatment-emergent adverse event
TMS	Transcranial magnetic stimulation
US	United States
V	Visit
VAS	Visual Analog Scale
VNS	Vagus nerve stimulation
W	Week
WHO-DD	World Health Organization drug dictionary
YMRS	Young Mania Rating Scale

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Enrolled Subject	Any subject who signed the study specific informed consent and was dispensed study drug.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and/or active control.
Treatment Period	The period of the study in which the study drug is administered.
Completed Subject	Any subject who participated throughout the duration of the treatment period, up to and including Visit 15E.
Early Termination	Any subject who was successfully enrolled into the open-label treatment period of the study but did not complete the study.
End of Treatment	The day that the subject receives the protocol-defined last dose of the study drug.

4. INTRODUCTION

4.1. Background

The treatment of bipolar depression is challenging, due to the complexity of clinical presentations, which may include mixed symptoms with depression predominating. Although the pharmacologic treatment of bipolar depression is dominated by 3 major classes of drugs, the atypical antipsychotics, anticonvulsants, and serotonergic antidepressants, these treatments have significant limitations including undesirable side effects such as metabolic derangement, weight gain, sedation, sexual dysfunction, akathisia, and extrapyramidal effects (Kemp 2014).

Amisulpride has been shown in a large meta-analysis of 32 oral antipsychotics, to be associated with relatively little weight gain (Huhn 2019). The clinical efficacy of amisulpride on depressive symptoms in mood disorders (Montgomery 2002) has been demonstrated at dose levels associated with relatively low dopamine D_2 receptor occupancy. Racemic amisulpride is approved in Italy, Czech Republic, and Portugal for the treatment of dysthymia at a low dose of 50 mg/day (Lecrubier 1997), which is substantially lower than the 400-800 mg/day dose recommended for the treatment of schizophrenia (Solian SMPC 2021). *In vitro* radioligand binding studies show that racemic amisulpride has high affinity for serotonin 5-HT_7 receptors in addition to dopamine D_2 receptors (Abbas 2009). Preclinical pharmacology studies using 5-HT_7 knockout mice suggest that the antidepressant-like effects of amisulpride are mediated by 5-HT_7 receptor antagonism (Abbas 2009).

SEP-4199 is a non-racemic mixture of aramisulpride and esamisulpride enantiomers in an 85:15 ratio. Aramisulpride is stereoselective for antagonism of serotonin 5-HT_7 receptors. Esamisulpride is stereoselective for antagonism of dopamine D_2 receptors. The 85:15 ratio of R:S enantiomers of SEP-4199 is optimal for maximizing serotonergic 5-HT_7 receptor antagonism in a dose range that retains < 50% D_2 receptor occupancy. SEP-4199 leverages the potential antidepressant activity of racemic amisulpride, driven by 5-HT_7 receptor antagonism, from the D_2 receptor-mediated antipsychotic activity by discovering that each enantiomer favors a different receptor (Hopkins 2021). Therefore, the pharmacology of SEP-4199 is designed to treat depressive symptoms via 5-HT_7 antagonism, and to confer some of the mood stabilizing benefits of limited D_2 antagonism while reducing the risk of side effects such as extrapyramidal symptoms and akathisia which are associated with higher levels of D_2 antagonism.

4.2. Study Conduct Rationale

This study is being conducted to evaluate the long-term safety, tolerability, and effectiveness of open-label treatment with SEP-4199 controlled release (CR) dosed flexibly at 200 mg/day or 400 mg/day, in subjects who previously completed a 6-week double-blind placebo-controlled lead-in study of SEP-4199 CR (hereinafter referred to as lead-in study of SEP-4199 CR) for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression).

4.3. Risk-Benefit Assessment

To date, one completed Phase 2 6-week clinical study (SEP380-201) evaluated fixed doses of SEP-4199 Immediate Release (IR) formulation at doses of 200 mg/day and 400 mg/day vs. placebo in subjects with bipolar I depression. In the full global intention-to-treat (ITT)

population, including North American, Latin American, European, and Japanese subjects (N = 337), both SEP-4199 IR 200 mg/day and 400 mg/day doses demonstrated significantly greater improvement compared to placebo (post-hoc adjusted p = 0.025 for both treatment groups using the same multiplicity adjustment approach as for the primary analysis). Based on the full global safety population, SEP-4199 IR was well tolerated in this study, with an overall adverse event (AE) rate (< 50%) in both dose groups that was comparable to that in the placebo group and a low rate (< 9% in either group) of discontinuations due to an AE. These results demonstrated proof of concept for the efficacy of SEP-4199 IR in the treatment of bipolar I depression and support further development of the SEP-4199 compound. However, safety and tolerability data for SEP-4199 IR in patients with bipolar I depression are currently limited to those collected over the 6-week treatment duration. Longer-term exposure to clinical doses of SEP-4199 is needed to fully evaluate safety, tolerability, and effectiveness.

A novel CR formulation of SEP-4199 has been developed. SEP-4199 CR was well tolerated in the PK and positron emission tomography (PET) imaging study in healthy volunteers (SEP380-105). Administration of SEP-4199 CR resulted in the same degree of dopamine D_2 receptor occupancy after multiple doses as did SEP-4199 IR at the same dosages, while exhibiting lower serum concentrations at C_{max}. The lower C_{max} of SEP-4199 CR was associated with substantially less QT interval corrected for heart rate (QTc) interval prolongation than was observed with SEP-4199 IR. Therefore, SEP-4199 CR is hypothesized to be therapeutically equivalent to SEP-4199 IR, but with an improved therapeutic index due to improved cardiac safety. For this reason, the SEP-4199 CR formulation will be evaluated in the current long-term open-label study.

5. 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 a lead-in study of SEP-4199 CR for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression).

5.1. 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).

5.2. Additional 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).

5.3. 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).

5.4. Pharmacokinetic and 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.

6. STUDY ENDPOINTS

6.1. Safety Endpoints

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

6.2. 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

6.3. Pharmacokinetic and Pharmacodynamic Endpoints

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

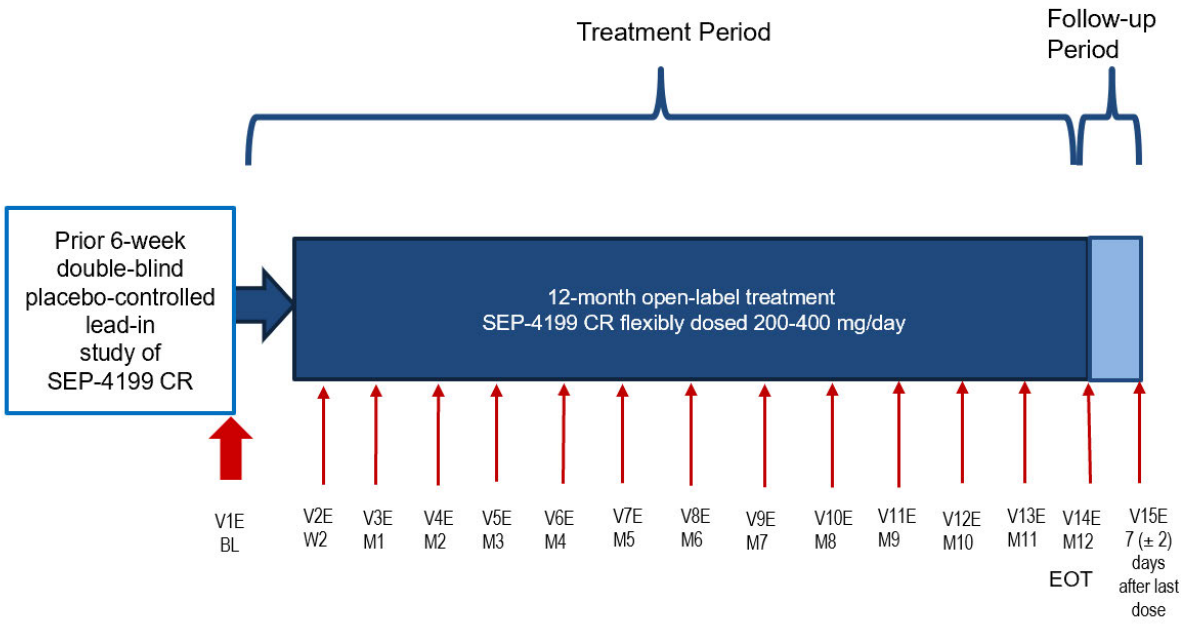
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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.

Figure 1: Study Schematic



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

Baseline (Visit 1E; Day -1)

Visit 6/End of Treatment (EOT) (Day 42) of the lead-in study of SEP-4199 CR will serve as the Baseline visit of the current open-label extension study. Subjects who completed 6 weeks of double-blind treatment in a lead-in study of SEP-4199 CR and who meet eligibility criteria to continue into the current extension study may be enrolled. Baseline values for safety and

effectiveness measures for this study will be carried over from Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR for each subject. Subjects should continue dosing with SEP-4199 CR in the current open-label study without dosing interruption.

Open-Label Treatment Period (Day 1 to Visit14E/Month 12)

Subjects will self-administer the study drug on an outpatient basis once daily beginning on Day 1 and continue for 12 months. Subjects will be instructed to administer study drug as a single oral dose in the morning at approximately the same time each day. The last dose of study drug will be self-administered by the subject at home on the morning of Visit 14E (Month 12).

During the open-label treatment period, subjects will have clinic visits at Week 2/Day 14 and Months 1 to 12. In order to facilitate scheduling of clinic visits and telephone calls, a window of ± 2 days will be allowed for Visits 2E (Week 2/Day 14) and 3E (Month 1); a window of ± 5 days will be allowed for Visits 4E (Month 2) to 13E (Month 11), and a window of +5 days will be allowed for Visit 14E (Month 12). Between study visits, subjects will be contacted weekly by telephone.

All subjects will initiate treatment with SEP-4199 CR 200 mg/day. The dose may be increased to 400 mg/day at Visit 2E (Week 2/Day 14) or later, based on the Investigator's judgment. However, if clinically indicated, the dose may be increased as early as Day 7 at an unscheduled visit. The dose may be decreased to 200 mg/day at any time thereafter for tolerability. If a dose decrease is needed between study visits, subjects will return to the clinic for an unscheduled visit for drug dispensation. Dose increases will occur only at scheduled or unscheduled clinic visits. Prior to a dose increase, safety assessments will be completed, including but not limited to evaluation of AEs, concomitant medications, vital signs, and ECGs. Subjects whose ECG results, based on machine reading, show increase from Baseline in QT interval corrected for heart rate using Fridericia's formula (QTcF) interval ≥ 30 milliseconds (msec) or whose QTcF interval is ≥ 480 msec at the 200 mg/day dose are not allowed to have their dose increased to 400 mg/day. Subjects with hyperprolactinemia-related AESI are not allowed to have their dose increased to 400 mg/day.

End of Treatment (EOT)/Early Termination (ET) (Visit 14E: Month 12)

Subjects will have Visit 14E at Month 12 (+ 5 days) for EOT assessments of safety and effectiveness.

Subjects who prematurely discontinue from the study will undergo an ET visit to include all Visit 14E assessments and procedures.

Follow-up Period (Visit 15E, 7 [± 2] days after last dose)

All subjects will have a follow-up visit for safety and tolerability assessments 7 (± 2) days after their last dose of study drug. Assessment of potential withdrawal effects will also be made during the follow-up period.

7.2. Treatment Assignment and Blinding

This is an open-label study; therefore, randomization and blinding will not be employed. All subjects will receive flexible dosing with SEP-4199 CR 200 mg/day or 400 mg/day.

Prolactin values at open-label Baseline visit (including any repeat testing) will be masked in the lab data transfer until the study database of the lead-in study of SEP-4199 CR is locked and treatment is unblinded for all subjects. Prolactin values assessed after the first dose of study drug of the open-label treatment period will not be masked and will appear in the regular lab data transfer.

Plasma concentrations of aramisulpride, esamisulpride, and total amisulpride will not be disclosed before the study database of the lead-in study of SEP-4199 CR is locked and treatment is unblinded for all subjects.

7.3. Rationale

7.3.1. Rationale for the Study Design

This study is being conducted to evaluate the long-term safety, tolerability, and effectiveness of open-label treatment with SEP-4199 CR dosed flexibly at 200 mg/day or 400 mg/day, in subjects who previously completed a lead-in study of SEP-4199 CR for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression).

To date, one completed Phase 2 6-week clinical study (SEP380-201) evaluated fixed doses of SEP-4199 IR formulation at doses of 200 mg/day and 400 mg/day vs. placebo in subjects with bipolar I depression. In the full global ITT population, including North American, Latin American, European, and Japanese subjects (N = 337), both SEP-4199 IR 200 mg/day and 400 mg/day doses demonstrated significantly greater improvement compared to placebo (post-hoc adjusted $p = 0.025$ for both treatment groups using the same multiplicity adjustment approach as for the primary analysis). Based on the full global safety population, SEP-4199 IR was well tolerated in this study, with an overall AE rate (< 50%) in both dose groups that was comparable to that in the placebo group and a low rate (< 9% in either group) of discontinuations due to an AE. These results demonstrated proof of concept for the efficacy of SEP-4199 IR in the treatment of bipolar I depression and support further development of the SEP-4199 compound. However, safety and tolerability data for SEP-4199 IR in patients with bipolar I depression are currently limited to those collected over the 6-week treatment duration. Longer-term exposure to clinical doses of SEP-4199 is needed to fully evaluate safety, tolerability, and effectiveness.

A novel CR formulation of SEP-4199 has been developed. SEP-4199 CR was well tolerated in the PK and PET imaging study in healthy volunteers (SEP380-105). Administration of SEP-4199 CR resulted in the same degree of dopamine D_2 receptor occupancy after multiple doses as did SEP-4199 IR at the same dosages, while exhibiting lower serum concentrations at C_{max}. The lower C_{max} of SEP-4199 CR was associated with substantially less QTc interval prolongation than was observed with SEP-4199 IR. Therefore, SEP-4199 CR is hypothesized to be therapeutically equivalent to SEP-4199 IR, but with an improved therapeutic index due to improved cardiac safety. For this reason, the SEP-4199 CR formulation will be evaluated in the current long-term open-label study.

7.3.2. Rationale for the Dosages

The current extension study will enroll subjects who previously completed a lead-in study that evaluated SEP-4199 CR monotherapy at fixed doses 200 mg/day or 400 mg/day vs. placebo. Therefore, this study will continue to evaluate the longer-term safety, tolerability, and

effectiveness of open-label SEP-4199 CR monotherapy, flexibly dosed at 200 mg/day or 400 mg/day.

7.3.3. Rationale for the Study Population

Only subjects who complete a lead-in study that evaluates SEP-4199 CR monotherapy at fixed doses of 200 mg/day or 400 mg/day vs. placebo will be included in this extension study.

7.3.4. Rationale for the Endpoints

The standard safety assessments and their timing are appropriate to assess the safety of SEP-4199 CR in adults with bipolar I depression. The symptom, functional, and quality of life assessments were selected to address the potential effectiveness of SEP-4199 CR on these parameters.

7.4. Prevention of Missing Data

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

- Specific medications for the as needed (PRN) treatment of movement disorders and acute extrapyramidal symptoms (EPS) are permitted.
- Specific medications for the PRN treatment of anxiety/agitation and insomnia are permitted.
- Training the sites on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial.
- The Sponsor will use study centers with a good track record of enrolling and following eligible subjects.
- Monitor data collection for adherence during the study.

Details for data handling rules of missing data will be provided in the Statistical Analysis Plan (SAP).

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

The subjects who fulfill the following criteria will be included in the study:

1. Subject provides written informed consent and is willing and able to comply with the protocol in the opinion of the Investigator.
2. Subject has completed 6 weeks of double-blind treatment and all scheduled assessments from Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR.
3. Subject is medically appropriate for long-term open-label treatment with SEP-4199 CR in the opinion of the Investigator.
4. Female subjects of childbearing potential must agree to use effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken. In the Investigator's judgment, the subject will adhere to this requirement. Contraception requirements are detailed in Section 10.4.
5. Male subjects agree to avoid fathering a child and to use effective methods of birth control throughout the study and until at least 90 days after the last study drug administration. Contraception requirements are detailed in Section 10.4.

8.2. Subject Exclusion Criteria

The subjects who meet any of the following criteria will be excluded from the study:

1. Subject is at high risk of non-compliance in the opinion of the Investigator.
2. Subject plans to initiate treatment with a prohibited psychotropic medication during the study.
3. Subject plans to initiate treatment with transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), or deep brain stimulation (DBS) during the study.
4. Subject experienced a moderate or severe hyperprolactinemia-related AESI in the lead-in study of SEP-4199 CR.
5. Subject will require treatment with a drug that is associated with increases in QTc interval (see Section 23, Appendix IV for a list of medications, not all inclusive).
6. Subject had any of the following at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR based on machine reading:
    - increase in QTcF interval of ≥ 30 msec from Baseline of the lead-in study of SEP-4199 CR AND a QTcF interval ≥ 480 msec
    - increase in QTcF interval ≥ 60 msec from Baseline of the lead-in study of SEP-4199 CR
    - QTcF interval > 500 msec
    - treatment-emergent clinically significant ECG abnormality.

7. Subject is considered by the Investigator to be at imminent risk of suicide or injury to self or others, has a MADRS item 10 (suicidal ideation) score ≥ 4, or answers "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR.
8. Female subject of child-bearing potential has a positive urine pregnancy test at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR or plans to become pregnant during the current study.
9. Subject tests positive for any drug of abuse or cannabis at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

SEP-4199 CR will be supplied as 200 mg tablets containing a fixed 85:15 ratio of aramisulpride:esamisulpride.

- For the SEP-4199 CR 200 mg/day dose, study drug will consist of 1 x 200 mg tablet.
- For the SEP-4199 CR 400 mg/day dose, study drug will consist of 2 x 200 mg tablets.

A description of the investigational product is provided in Table 5.

Table 5: Investigational Product

Attribute	Investigational Product
Product name	SEP-4199 CR 200 mg
Dosage form	Tablets
Unit dose	Tablet
Route of administration	Oral
Physical description	Pale orange round film-coated unmarked tablets
Excipients	D-Mannitol, partly pregelatinized starch, partially hydrolyzed polyvinyl alcohol, hypromellose, light anhydrous silicic acid, sodium stearyl fumarate, Macrogol 400, titanium oxide, talc, ferric oxide yellow, red ferric oxide, and carnauba wax

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

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.

9.2.2. Labeling Description

All packaging for the study medications will be labeled with:

- Protocol number
- Sponsor's name and address
- Compound/Code or name of investigational drug and dosage form
- Content (eg, number of tablets)
- Investigational New Drug statement/caution statement
- Instructions for use and storage

- Batch number
- Period of use (as required)
- Blank space to record visit number
- Blank space for subject identifiers
- Unique medication number/kit ID number
- Investigator information (if needed)

9.3. Study Drug Storage

All study drug should be stored at 15°C to 25°C (59°F to 77°F) and away from light. Excursions of 9°C to 30°C (48°F to 86°F) are permitted during shipment of study drug to investigational sites. The subject will be instructed to store the medication at room temperature.

9.4. Dispensing of Study Drug

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

Study drug blister cards will be assigned by the IXRS based on the treatment schedule. The IXRS will generate instructions for which blister card ID(s) to dispense to a subject. 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 (see Table 2).

The first study drug dose will be taken on Day 1. Subjects will take one or two tablets of study drug according to dosing instructions once a day in the morning at approximately the same time each day. Study drug may be taken with or without food.

9.5. Study Drug Accountability

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

Upon receipt of study drug, the Investigator or designee will inspect the supplies and verify receipt of the shipment in the IXRS, confirming the date of receipt, inventory, and condition of study drug received.

The IXRS will also be used for the accountability of the study drug at the clinical site. The Investigator or designee will maintain records for accountability within the IXRS, including study drug dispensation, return, and availability of study drug received. The Investigator or designee will collect and document all used and unused study drug from study subjects at appropriate study visits.

9.6. Study Drug Handling and Disposal

The Investigator or designee is responsible for storing the study drug in a secure location. Study drug should be maintained under the strict control of qualified staff at all times. Proper handling and storage guidelines should be followed.

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

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

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

10. TREATMENT OF SUBJECTS

10.1. Study Medication

SEP-4199 CR 200 mg tablets for 200 mg and 400 mg doses will be supplied as described in Section 9.1.

Study drug will be self-administered by the subject once daily as a single oral dose in the morning at approximately the same time, beginning on Day 1 and continuing through Visit 14E (Month 12).

10.1.1. Dose Adjustment Criteria

All subjects will initiate treatment with SEP-4199 CR 200 mg/day. The dose may be increased to 400 mg/day at Visit 2E (Week 2/Day 14) or later, based on the Investigator's judgment. However, if clinically indicated, the dose may be increased as early as Day 7 at an unscheduled visit. The decision to increase the dose and dispense additional study drug will be made by the Investigator at a scheduled or unscheduled study visit. A dose decrease can occur at any time for safety or tolerability concerns (minimum dose of 200 mg/day). If a dose decrease is needed between study visits, subjects will return to the clinic for an unscheduled visit for drug dispensation. Temporary interruption of the study drug is allowed at the Investigator's discretion for specific hyperprolactinemia-related AESI (see Section 13.1).

Prior to a dose increase, safety assessments will be completed, including but not limited to evaluation of adverse events, concomitant medications, vital signs, and ECGs. Subjects whose ECG results, based on machine reading, show increase from Baseline in QTcF interval $\geq$ 30 msec or whose QTcF interval is $\geq$ 480 msec at the 200 mg/day dose are not allowed to have their dose increased to 400 mg/day. Subjects with hyperprolactinemia-related AESI are not allowed to have their dose increased to 400 mg/day. IXRS drug dispensing guidelines should be followed for dispensing the drug to subjects. A specific user manual will be provided.

10.2. Treatment Compliance

Compliance must be monitored closely and evaluated by the Investigator at each visit. Subjects will be instructed to bring all used blister cards and unused study drug with them to each visit. The number of tablets lost, if any, needs to be reported and recorded. Compliance for a study visit period will be assessed by counting the number of returned tablets, calculated by dividing the actual number of doses taken (= number of tablets dispensed – number of tablets returned – number of tablets lost per tablet count) by the number of doses the subject should have taken and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study drug.

Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant. Evidence of noncompliance must be immediately reported to the Clinical Research Associate (CRA) and/or Medical Monitor.

10.3. Concomitant Medications and Therapies

Any medication, vaccination, or non-pharmacological therapy that is taken by or administered to the subject between signing of informed consent and final visit will be recorded in the electronic

case report form (eCRF). The entry must include the dose, frequency, route, indication, and dates of use.

Concomitant medications in the lead-in study of SEP-4199 CR that were ongoing at Visit 6/EOT (Day 42) will be entered into the eCRF for this study (SEP380-303). All changes in concomitant medications or new medications administered during the study up to the Follow-up Visit (7 ± 2 days after last dose) will be recorded.

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

Ongoing treatment or initiation of treatment with non-pharmacologic psychotherapy is allowed.

10.3.1. Prohibited Medications

Treatment with other psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) is prohibited except as noted below.

The use of herbal supplements or other complementary or alternative medications during the trial is not permitted.

10.3.2. Concomitant Non-psychotropic Medications

Medications for the short-term (no more than 10 days) treatment of an acute medical condition are allowed, provided that the medications do not prolong the QTc interval. Section 23, Appendix IV provides a representative, but not exhaustive, list of medications that prolong the QT interval and are not allowed during the study. Non-psychotropic medications may be used to treat mild, chronic medical conditions. β-adrenergic antagonists used to treat stable hypertension may be continued. In addition, non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol, ibuprofen) are allowed during the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study medication. Routine vaccines (ie, seasonal influenza, pneumonia, COVID-19, etc.) are allowed based on Investigator judgement.

10.3.3. Concomitant Psychotropic Medications

Medications for treatment of movement disorders may be administered if symptoms emerge. Benztropine (≤ 6 mg/day), biperiden (≤ 16 mg/day), trihexyphenidyl (≤ 15 mg/day), or diphenhydramine (≤ 100 mg/day) are permitted as needed to treat extrapyramidal symptoms. Propranolol (≤ 120 mg/day) or amantadine (≤ 300 mg/day) are permitted as needed to treat akathisia.

Concomitant use of anxiolytics, sedatives, and hypnotics is permitted with the following restrictions: Lorazepam is permitted up to 2 mg/day for intolerable anxiety/agitation. Lorazepam (≤ 2 mg/day), eszopiclone (≤ 3 mg/day), zopiclone (≤ 7.5 mg/day), zolpidem (≤ 10 mg/day), zolpidem CR (≤ 12.5 mg/day), and temazepam (≤ 30 mg/day) may be administered at bedtime for insomnia, as needed. Hypnotic agents should be administered no more than once nightly and should not be used in combination.

In regions that do not have the above specified medications available, similar medications at equivalent dosages may be permitted after consultation with and approval by the Medical Monitor.

Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor.

10.4. Contraception Requirements

Female subjects who participate in this study must be of:

- Non-childbearing potential (ie, physiologically incapable of becoming pregnant), which includes:
  - Women who have had a hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation, or bilateral tubal occlusion (as determined by subject's medical history)

    OR
  - Postmenopausal females, defined as at least 12 months of spontaneous amenorrhea and confirmed by follicle stimulating hormone (FSH) concentrations within postmenopausal range at Visit 1 (Screening) of the lead-in study of SEP-4199 CR as determined by the central laboratory

-OR-

- Childbearing potential with a negative urine pregnancy test at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR and satisfying one of the following requirements:
  - Completely abstinent from intercourse as part of the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and the withdrawal method are not acceptable methods of contraception. Subject must have been abstinent for at least 60 days prior to administration of the first dose of study drug, throughout the Treatment Period and for a minimum of 30 days after completion or premature discontinuation from the study drug.
  - Use of effective methods of contraception during the Treatment Period and for 30 days after last dose of study drug. Effective forms of contraception include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
    - Implanted intrauterine device;
    - Implanted intrauterine hormone-releasing system;
    - Vasectomized partner (provided that partner is the sole sexual partner).

- Two barrier methods used in combination (eg, condom and spermicide or diaphragm with spermicide). Note: a female condom and a male condom should not be used together due to friction between the 2 barrier methods reducing effectiveness of contraception.
- Women using hormonal contraception must be supplemented with a barrier method (preferably male condom).

Post-coital methods of contraception are not permitted.

Male subjects with a female partner(s) of childbearing potential must agree to avoid fathering a child and either must be surgically sterile (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), completely abstinent, or use effective methods of contraception throughout the study and for at least 90 days after the last dose of study drug. Male subjects must also refrain from donation of semen/sperm throughout the study and for 90 days after last dose of the study drug. Female subjects are not allowed to donate eggs throughout the study and up to 30 days after the last dose of study drug.

10.5. Guidance for Overdose

The effects of an overdose of SEP-4199 are unknown and there is no known treatment in case of overdose. Standard symptom support measures should be used in the case of excessive pharmacological effects or overdose.

11. STUDY ASSESSMENTS

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

11.1. Duplicate Subject Check

The Verified Clinical Trials LLC ("VCT") Research Subject Database ("VCT Registry") is used at study sites to help determine whether a subject is already participating in or has recently participated in another clinical trial. Subjects will be given detailed information about the processing of their personal data through the VCT Registry in a separate patient information and consent form (Verified Clinical Trials LLC Research Subject Database Declaration of Consent for the Processing of Personal Data) during the lead-in study of SEP-4199 CR and will be asked to give explicit consent by signing this separate patient information and consent form to continue to be monitored while participating in SEP380-303, where allowed under local laws and regulations. No personal data will be entered into or processed through the VCT Registry unless the relevant subject has given explicit consent.

11.2. Demographics and Baseline Characteristics

Demographics (date of birth, age, sex, ethnicity, race) and medical and psychiatric history collected in the lead-in study of SEP-4199 CR will be utilized for this study. Date of birth, age, and sex will be re-entered into the eCRF of this study.

11.3. Effectiveness Assessments

For all efficacy assessments, the open-label Baseline values are carried over from Visit 6/EOT (Day 42) assessments collected in the lead-in study of SEP-4199 CR.

11.3.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated assessment of the subject's level of depression. The MADRS consists of 10 items that measure Apparent Sadness, Reported Sadness, Inner Tension, Reduced Sleep, Reduced Appetite, Difficulty Concentrating, Lassitude, Inability to Feel, Pessimistic Thoughts, and Suicidal Thoughts. Each item is scored from 0 to 6, with higher scores indicating greater symptom severity.

The MADRS will be administered by a trained and qualified rater. The MADRS interviews will be audio recorded and the recording will be reviewed by the Sponsor's designee to monitor the quality of the rater interviews, where allowed by local/regional regulations. No identifying information should be collected with the audio recording. Further information regarding administration of the MADRS, including rater training and certification as well as recording of MADRS scores, will be provided in the Study Reference Manual.

11.3.2. Clinician Global Impression-Bipolar Version-Severity of Illness (CGI-BP-S)

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

Further information regarding administration of the CGI-BP-S, including rater training and certification as well as recording of CGI-BP-S scores, will be provided in the Study Reference Manual.

11.3.3. Hamilton Anxiety Rating Scale (HAM-A)

The 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. The Structured Interview Guide for the HAM-A (SIGH-A) will be used for administration of the HAM-A.

Further information regarding administration of the HAM-A, including rater training and certification as well as recording of HAM-A scores will be provided in the Study Reference Manual.

11.3.4. Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR16)

The QIDS-SR16 is a 16-item subject-reported depression symptom severity questionnaire. The scoring of the QIDS-SR16 converts responses to 16 separate items into the 9 DSM-IV symptom criterion domains. The total score ranges from 0-27 with higher scores indicating greater severity. The 9 domains are: sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (early/middle/late insomnia or hypersomnia), decrease/increase in appetite/weight, and psychomotor agitation/retardation.

Site staff will assist the subject in the initiation of the QIDS-SR16 assessment. Clinical staff will not participate in the administration of the QIDS-SR16 after initiation. Further information regarding administration of the QIDS-SR16, including recording of scores, will be provided in the Study Reference Manual.

11.3.5. Sheehan Disability Scale (SDS)

The 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).

Further information regarding administration of the SDS, including rater training and certification as well as recording of SDS scores, will be provided in the Study Reference Manual.

11.3.6. EuroQol - 5 Dimension - 5 Level (EQ-5D-5L)

The EQ-5D-5L is a subject self-reported, 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 a descriptive system and the EuroQol Visual Analogue Scale (EQ-VAS).

The descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the subject's health state.

The EQ-VAS records the subject's self-rated health on a vertical visual analogue scale, where the endpoints are labeled "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 reflects the subject's own judgment.

11.3.7. Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS (Snaith 1995) 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. Subjects are asked to respond based on their ability to experience pleasure in the past few days. Each of the 14 questions is in the form of the statement "I would enjoy_____" and asks the subject to choose between the choices: strongly disagree, disagree, agree, or strongly agree.

11.4. Safety Assessments

11.4.1. Adverse Events

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

Adverse events in the lead-in study of SEP-4199 CR that were ongoing at Visit 6/EOT (Day 42) will be entered into the eCRF for this study (SEP380-303). All changes in adverse events or new adverse events occurring during the study up to the Follow-up Visit will be recorded.

11.4.2. Clinical Laboratory Tests

Subjects are required to fast for at least 8 hours prior to sample collection for laboratory testing at Visit 2E, Visit 4E, Visit 6E, Visit 8E, Visit 10E, Visit 12E, and Visit 14E (EOT/ET); fasting is also required at Week 6 (EOT) in the lead-in study of SEP-4199 CR, which serves as baseline (Visit 1E) in this long-term safety study. The clinical laboratory tests required by protocol are listed in Section 21, Appendix II.

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be conducted centrally unless an exception is approved by the Medical Monitor. The site must notify the Medical Monitor as soon as possible when performing unscheduled laboratory tests.

Point of care (POC) testing will be used for the urine pregnancy test and rapid urine drug test. A serum pregnancy test should be submitted to the central lab for any positive urine pregnancy test, and a urine drug screen should be submitted to the central lab for any positive rapid urine drug test throughout the study.

For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

11.4.3. Vital Signs

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

Respiratory rate and temperature will also be measured, and all measurements will be recorded in the eCRF.

Weight will be measured in street clothes, without shoes and coat/jacket. BMI will be calculated in the analysis. Waist circumference will also be measured.

Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

Clinically significant changes from signing the informed consent form (ICF) in vital sign parameters, as determined by the Investigator, will be noted as AEs in the eCRF.

11.4.4. Centrally-read ECG

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 10 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples, with the exception of fasting blood draws. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a central facility, according to established quality assurance procedures for inter/intra reader variability. Refer to Section 20, Appendix I for additional information. ECG parameters to be collected include ventricular heart rate (beats/min), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec) and centrally-read overall ECG interpretation (Normal; Abnormal, insignificant; Abnormal, potentially significant; Abnormal, significant) including type of abnormality, if present. QTcF and QT interval corrected for heart rate using Bazett's formula (QTcB) will also be reported.

11.4.5. Neurological and Physical Examination

Complete physical examination as well as neurological examination will be performed. The physical examination includes an assessment of general appearance and a review of systems

(dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems). The neurological examination includes an assessment of general appearance, mental status, cranial nerves, motor system, sensory system, reflexes, coordination, and gait.

Any clinically significant changes from signing of the ICF, as determined by the Investigator, will be noted as AEs in the eCRF.

11.4.6. Safety Scales

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

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (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 will be administered by a trained rater at the site.

This study will utilize the "Since Last Visit" version of the C-SSRS.

Subjects who answer "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on any post-Baseline C-SSRS assessment must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves; in addition, an associated AE must be reported.

Further information regarding administration of the C-SSRS, including rater training and certification as well as recording of C-SSRS scores, will be provided in the Study Reference Manual.

11.4.6.2. 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 will be administered by a qualified rater at the site. Further information regarding administration of the YMRS, including rater training and qualification as well as recording of YMRS scores, will be provided in the Study Reference Manual.

Treatment-emergent mania or hypomania is defined as a YMRS total score ≥ 16 at any 2 consecutive post-Baseline visits or at the final visit, or an AE of mania or hypomania.

11.4.6.3. 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 for instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions including the facial area, extremities, and trunk. There are 2 items related to dental status, as well as 3 global impression items assessing overall severity,

incapacitation, and the subject's awareness of abnormal movements (Guy 1976, Munetz 1988). The AIMS raters will be required to meet specific credential and educational criteria before they are certified to rate for this study.

Further information regarding administration of the AIMS, including rater training and certification as well as recording of AIMS scores, will be provided in the Study Reference Manual.

11.4.6.4. Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale intended for the assessment of neuroleptic-induced akathisia. It consists of 4 items, including one item assessing objective restlessness, 2 items assessing subjective restlessness (awareness and related distress), and one global clinical assessment item. All items are anchored and utilize a 4-point scale, except for the global rating which uses a 6-point scale (from absence of akathisia through severe akathisia). The subjective and objective items are summed to yield a total score. The BARS can be administered in about 10 minutes (Barnes 1989, Barnes 2003, Schooler 2000).

Further information regarding administration of the BARS, including rater training and certification as well as recording of BARS scores, will be provided in the Study Reference Manual.

11.4.6.5. Modified Simpson-Angus Scale (SAS)

The modified SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale, and address rigidity, gait (bradykinesia), tremor, glabellar tap, and salivation (Simpson 1970).

Further information regarding administration of the modified SAS, including rater training and certification as well as recording SAS scores, will be provided in the Study Reference Manual.

11.4.6.6. 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 is used to evaluate symptoms of withdrawal after discontinuation of study medication. Symptoms are assessed as present or absent; if present, then intensity is assessed as mild, moderate, or severe.

11.5. Pharmacokinetic Assessments

Blood samples will be collected for population pharmacokinetics and plasma prolactin at the following visits: Visit 2E (Week 2/Day 14), Visit 4E (Month 2), Visit 6E (Month 4), Visit 8E (Month 6), Visit 10E (Month 8), Visit 12E (Month 10), Visit 14E (Month 12), and Follow-up (Visit 15E, 7 ± 2 days after last dose). See Section 22, Appendix III for sample collection and handling guidelines.

Prior to PK blood sample collection, subjects will record the date and time of their 3 most-recent study drug doses; the clinical site staff will record the dates and times of the 3 doses in the eCRF for each of the PK collection visits during the treatment period.

Plasma samples will be analyzed for concentrations of aramisulpride and esamisulpride using a validated enantioselective liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Plasma samples will also be analyzed for prolactin concentrations by an enzyme-linked immunosorbent assay (ELISA).

Remaining plasma samples after amisulpride PK and prolactin analysis 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.

11.6. Study Visits and Assessments

To ensure subject safety and data integrity, should circumstances warrant and with Sponsor approval, remote site/subject visits may be conducted.

11.6.1. Visit 1E: Baseline (Day -1)

The Open-Label Baseline visit of the present study is on the same day as Visit 6/EOT (Day 42) in the lead-in study of SEP-4199 CR. Subjects will be evaluated at this visit to determine their eligibility for the study. The following study-related procedures will be performed at Visit 1E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Obtain informed consent, including signed informed consent for duplicate subject check (where local regulations allow).
- Review inclusion and exclusion criteria.
- Record subject demographics.
- Review concomitant medications. 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.
- Record adverse events. 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.
- Dispense study drug. Instruct the subject to administer study drug as a single oral dose in the morning at approximately the same time each day beginning the following day (Day 1).
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

The following procedures conducted at Visit 6/EOT (Day 42) of the lead-in study of SEP-4199 CR do not need to be repeated for the Open-Label Baseline visit of this study:

- Physical and neurological examinations

- Vital sign measurements
- Weight
- Waist circumference
- 12-lead ECG
- Blood samples for the following laboratory tests (Subjects must have fasted for at least 8 hours.):
  - Hematology and Serum Chemistry
  - Thyroid Panel
  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - High-sensitivity C-Reactive Protein (hs-CRP)
- Blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Urine sample for rapid urine drug test, urinalysis, and urine pregnancy test (human chorionic gonadotropin [β-hCG], female subjects of childbearing potential)
- MADRS
- HAM-A
- YMRS
- QIDS-SR16
- SDS
- EQ-5D-5L
- SHAPS
- CGI-BP-S
- C-SSRS
- AIMS
- BARS
- SAS

11.6.2. Visit 2E (Week 2/Day 14 [± 2 days])

The following study-related procedures will be performed at Visit 2E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.
- Administer SAS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry
  - Serum Prolactin
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for urinalysis and rapid urine drug test.
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.

  - Instruct subject to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.3. Visit 3E (Month 1/Day 30 [± 2 days])

The following study-related procedures will be performed at Visit 3E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Perform 12-lead ECG.
- Collect urine sample for rapid urine drug screen and urine β-hCG (female subjects of childbearing potential).
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.4. Visit 4E (Month 2/Day 60 [± 5 days])

The following study-related procedures will be performed at Visit 4E; it is suggested that they be performed in the order presented below, as is possible by the site::

- Administer MADRS.
- Administer HAM-A.

- Administer YMRS.
- Administer CGI-BP-S.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.
- Administer SAS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry
  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - Thyroid Panel
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Dispense study drug.

  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.5. Visit 5E (Month 3/Day 90 [± 5 days])

The following study-related procedures will be performed at Visit 5E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Perform 12-lead ECG.
- Collect urine sample for rapid urine drug test and urine β-hCG (female subjects of childbearing potential).
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.6. Visit 6E (Month 4/Day 120 [± 5 days])

The following study-related procedures will be performed at Visit 6E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer HAM-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.
- Administer SAS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry
  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - Thyroid Panel
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Perform study drug accountability.

  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.7. Visit 7E (Month 5/Day 150 [± 5 days])

The following study-related procedures will be performed at Visit 7E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Perform 12-lead ECG.
- Collect urine sample for rapid urine drug test and urine β-hCG (female subjects of childbearing potential).
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.

  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.8. Visit 8E (Month 6/Day 180 [± 5 days])

The following study-related procedures will be performed at Visit 8E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer HAM-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.
- Administer SAS.
- Review concomitant medications.
- Record adverse events.
- Perform physical examination.
- Perform neurological examination.
- Obtain vital signs.
- Record weight.
- Record waist circumference.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry
  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin

  - hs-CRP
  - Thyroid Panel
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.9. Visit 9E (Month 7/Day 210 [± 5 days])

The following study-related procedures will be performed at Visit 9E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Perform 12-lead ECG.
- Collect urine sample for rapid urine drug test and urine β-hCG (female subjects of childbearing potential).

- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.10. Visit 10E (Month 8/Day 240 [± 5 days])

The following study-related procedures will be performed at Visit 10E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer HAM-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.
- Administer SAS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry

  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - Thyroid Panel
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.11. Visit 11E (Month 9/Day 270 [± 5 days])

The following study-related procedures will be performed at Visit 11E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.

- Record weight.
- Perform 12-lead ECG.
- Collect urine sample for rapid urine drug test, and urine β-hCG (female subjects of childbearing potential).
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.12. Visit 12E (Month 10/Day 300 [± 5 days])

The following study-related procedures will be performed at Visit 12E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer HAM-A.
- Administer YMRS.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.
- Administer SAS.
- Administer CGI-BP-S.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.

- Record weight.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry
  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - Thyroid Panel
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.13. Visit 13E (Month 11/Day 330 [± 5 days])

The following study-related procedures will be performed at Visit 13E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS.

- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Record weight.
- Perform 12-lead ECG.
- Collect urine sample for rapid urine drug test and urine β-hCG (female subjects of childbearing potential).
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.
  - Instruct subject to dose once daily in the morning at approximately the same time each day at home.
- Schedule next visit:
  - Instruct subject to administer the morning dose prior to the clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record the date and time of last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.
- Schedule weekly telephone check-in with subject.

11.6.14. Visit 14E (Month 12/Day 360 [+ 5 days]; End of Treatment/Early Termination)

The following study-related procedures will be performed at Visit 14E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer MADRS.
- Administer HAM-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer PWC.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer C-SSRS.
- Administer AIMS.
- Administer BARS.

- Administer SAS.
- Review concomitant medications.
- Record adverse events.
- Perform physical examination.
- Perform neurological examination.
- Obtain vital signs.
- Record weight.
- Record waist circumference.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.).
  - Hematology and Serum Chemistry
  - Serum Prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - hs-CRP
  - Thyroid Panel
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source and eCRF.
- Schedule Follow-up visit.

11.6.15. Follow-up: Visit 15E (7 ± 2 days after last dose)

All subjects will have a follow-up visit for safety and tolerability assessments 7 (± 2) days after their last dose of study drug. The following study-related procedures will be performed at Visit 15E; it is suggested that they be performed in the order presented below, as is possible by the site:

- Administer YMRS.

- Administer PWC.
- Administer C-SSRS.
- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Perform 12-lead ECG.
- Collect blood sample for serum prolactin.
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for rapid urine drug test and urine β-hCG (female subjects of childbearing potential).

11.6.16. Telephone Contacts

Telephone calls will be made weekly by a member of the research staff to the subject between scheduled study visits. The telephone calls will be used to collect AEs and concomitant medications, as well as to remind the subject about adherence to study drug administration and upcoming visits.

11.6.17. Unscheduled Visit for Dose Adjustment

11.6.17.1. Unscheduled Visit for Dose Increase

All subjects will initiate treatment with SEP-4199 CR 200 mg/day. The dose may be increased to 400 mg/day at Visit 2E (Week 2/Day 14) or later, based on the Investigator's judgment. However, if clinically indicated, a dose increase can occur as early as Day 7 at an unscheduled visit.

If a dose increase is needed between regularly scheduled visits, the subject will return to the clinic for an unscheduled visit. The following procedures will be conducted during this unscheduled visit for a dose increase:

- Review concomitant medications.
- Record adverse events.
- Obtain vital signs.
- Perform 12-lead ECG.
- Additional safety assessments are not required but may be performed based on the Investigator's judgment.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.

11.6.17.2. Unscheduled Visit for Dose Decrease

The dose may be decreased to 200 mg/day at any time for tolerability. If a dose decrease is needed between study visits, subjects will return to the clinic for an unscheduled visit. The following procedures will be conducted during this unscheduled visit for a dose decrease:

- Review concomitant medications.
- Record adverse events.
- Safety assessments are not required but may be performed based on the Investigator's judgment.
- Perform study drug accountability.
  - Collect used/unused drug and packaging.
- Dispense study drug.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

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

Untoward medical occurrences that occur after signing Study SEP380-303 ICF will be considered AEs.

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

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

12.1.2. Serious Adverse Events

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

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

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

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

as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

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

SAE criteria information will be captured on the eCRF.

12.1.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) collected during the study will include all hyperprolactinemia-related events, regardless of seriousness. Hyperprolactinemia-related AESI include, but are not limited to the following:

- Galactorrhea/breast discharge
- Breast disorders including gynecomastia, pain, swelling (moderate or severe events only)
- Lack of or delayed menorrhea, or other menstrual disorders
- Fractures/osteoporosis/osteopenia
- Sexual dysfunction in females and males including erectile dysfunction/changes in libido
- Any estrogen-related laboratory abnormality
- Prolactin-producing pituitary tumor
- Hirsutism

Subjects should be instructed to notify the clinical site within 24 hours if they develop any of the signs or symptoms noted above.

Subjects who develop any of the following AESI: amenorrhea (missed menses for a minimum of 3 months), symptomatic gynecomastia, or galactorrhea that does not resolve within 2 weeks of temporary study drug interruption or that recurs with re-challenge must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves. Re-challenge will be at the Investigator's discretion (see Section 13.1).

For AESI, if the event meets seriousness criteria, the Investigator will report the event to the Sponsor within 24 hours of the site being made aware of the event, as outlined in Section 12.4.1. AESI that do not meet seriousness criteria will be reported by the Investigator to the Sponsor within 5 business days of site awareness and in the same manner that SAEs are reported.

12.2. Objective Findings

Clinically significant changes from signing of the ICF in objective findings (eg, clinical laboratory value, ECG value, vital signs, and physical or neurological examination observation), as determined by the Investigator, will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as

the AE, not transaminase elevation). If a definite diagnosis is not available, then the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) will be recorded as the AE.

Clinical laboratory test results and ECG tracings and over-read reports will be reviewed, signed, and dated by the Investigator.

Any clinical laboratory value outside the normal range and any centrally over-read abnormal ECG finding will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether the value/finding is of clinical significance. Subjects with any clinically significant abnormal ECG finding at Visit 1E will be discontinued from the study (see Section 8.2). If a clinically significant laboratory or ECG abnormality is found after Visit 1E, during the study, and/or at the Follow-Up Visit, this should be recorded as an AE. Discontinuation due to AE with follow-up until resolution is mandatory for clinically significant ECG findings and hyperprolactinemia-related adverse events (see Section 13). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Additional laboratory and ECG testing during the study may be performed if medically indicated.

12.3. Collection and Recording of Adverse Events

All AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All AEs that occur from the signing of the informed consent to the subject's last visit must be recorded on the eCRF.

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

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

The severity of AE:

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

The frequency of AE:

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

The action taken with the study treatment:

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

The outcome of the AE:

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

The causal relationship of the AE to the study treatment: **Not related**

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

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

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

12.4. Immediately Reportable Events

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

- SAE

- Pregnancy

Additionally, AESI (defined in Section 12.1.3) that do not meet serious criteria must be reported to the Sponsor within 5 business days of the site's first awareness of the event.

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

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

Should the Investigator become aware of an SAE greater than 30 days post last dose, the Investigator or an authorized delegate should report SAEs "spontaneously" to PPD-Pharmacovigilance (PVG) if considered at least possibly related to the study drug.

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

An initial or follow-up SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG immediately but no more than 24 hours after the Investigator or study center staff become aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor provides the SAE form used to report SAEs.

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

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 30 days following the last dose of the study drug will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to discontinue the study drug. Further, the subject will be instructed to return to the study center within 48 hours of the first notification of pregnancy to the study center and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study drug. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth). Infants may be followed for up to one year following birth.

If a pregnancy is reported for a study subject's partner following the subject's first dose and up to 90 days following the last dose, the subject's partner may be asked to sign a consent form to allow the Sponsor to follow her pregnancy. The Sponsor's representative will provide instructions on how to collect pregnancy information in accordance with local requirements. Proper consent to collect the partner's information will be obtained before the collection of any information. Infants may be followed for up to one year following birth.

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

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

12.5. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will review safety data at regular intervals. The DSMB will be independent of the Sponsor, CRO, and the Investigators and will be empowered to recommend stopping the study due to safety concerns, but not for efficacy or futility. The membership of the DSMB and its mandate will be described in a separate DSMB charter.

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

13.1. Criteria for Subject Termination

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

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

- Adverse event
- Lack of efficacy (specify)
- Lost to follow-up (specify)
- Pregnancy
- Withdrawal of consent (specify)
- Non-compliance with study drug (specify)
- Protocol deviation (specify)
- Death
- Other (specify)

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

Discontinuation due to AE with follow-up until resolution is mandatory in the following cases:

- Subject who, at any study visit post-Baseline, has a QTcF interval > 500 msec, or who has a ≥ 60 msec increase in QTcF from Baseline (machine reading or centrally overread report), or who experiences a life-threatening cardiac arrhythmia must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves; in addition, an associated AE must be reported.
- Subject who develops an AE of amenorrhea (missed menses for a minimum of 3 months), symptomatic gynecomastia, or galactorrhea that does not resolve within 2 weeks of study drug interruption or that recurs with re-challenge must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves.
- Subject who answers “yes” to “suicidal ideation” item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on any post-Baseline C-SSRS assessment must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves; in addition, an associated AE must be reported.
- Subjects who require hospitalization/prolonged hospitalization for treatment of COVID-19-related illness will be discontinued. Subjects with an active COVID-19 infection should be discussed on a case-by-case basis with the IQVIA Medical

Monitor to obtain agreement on whether a subject with an active COVID-19 infection should be discontinued.

The reason for termination of study participation and information on the epoch will be recorded on the appropriate eCRF. In case of death, the date of death should be captured on the eCRF.

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

Subjects who discontinue prior to Visit 14E (Month 12) will undergo procedures and assessments scheduled for Visit 14E (Month 12) at the time of early discontinuation (see Section 11.6.14).

14. STUDY TERMINATION

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

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

In the event of study or site termination, subjects will undergo final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.6.14 and safety Follow-up Visit described in Section 11.6.15.

15. STATISTICS

15.1. Sample Size

Assuming a completion rate of 85% in lead-in study of SEP-4199 CR and an 80% rollover rate of completers from that study to the current extension study, it is estimated that approximately 355 subjects will be enrolled.

15.2. Statistical Hypotheses

Because of the nature of an open-labeled study, no statistical hypotheses are planned.

15.3. Analysis Populations and Analysis Groups

The safety population will include all subjects who receive at least one dose of study medication.

The follow-up population includes all subjects who receive at least one dose of study medication and have at least 1 assessment after the last study drug administration for any evaluation.

A total of 4 analysis groups will be formed based on a subject's previous participation in the lead-in study of SEP-4199 CR (previously randomized to SEP-4199 CR 200 mg/day, previously randomized to SEP-4199 CR 400 mg/day, previously randomized to any SEP-4199 CR dose group, previously randomized to placebo). A group that combines all of these analysis groups will also be presented.

15.4. Data Analysis

Summary tables, wherever applicable, will be presented by analysis group. Where changes are reported, the reference will be to the pretreatment Baseline from the lead-in study of SEP-4199 CR and indicated as "double-blind (DB) Baseline". Where relevant, changes from Baseline for the open-label study, defined as the Week 6 assessment in the double-blind study or the last assessment prior to the first dose of study medication in the open-label study, will also be reported, and will be referred to as the open-label study Baseline or "OL Baseline". Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, first quartile [Q1], third quartile [Q3], range, 95% confidence interval [CI] as needed) and categorical variables will be reported as frequencies and percentages at DB Baseline, OL Baseline, each of post-OL visit, and endpoint. No statistical comparisons will be conducted and no inferential statistics on effectiveness and safety will be presented.

15.4.1. Study Subject

Descriptive statistics of study subjects, including analysis population, subject disposition, demographic and Baseline characteristics, drug exposure and compliance, medical and psychiatric history at DB screening, prior and concomitant medications, and important protocol deviations, will be presented by analysis group for the Safety population. Important protocol deviations (IPDs) will be identified and documented based on a review of potentially IPDs prior to database lock. Details of the summary approaches for subject level information will provided in the SAP, and no further discussion is provided hereafter.

15.4.2. Effectiveness Analyses

Since this is an uncontrolled open-label extension of a lead-in study of SEP-4199 CR , no inferential statistics on efficacy will be presented. All effectiveness data will be summarized by analysis group based on the safety population.

Descriptive statistics of observed values and changes from DB Baseline and OL Baseline will be summarized by study visit and analysis group for effectiveness parameters (continuous). At a visit in the extension study, responders relative to DB Baseline are defined as those who show a 50% or more reduction (ie, improvement) from DB Baseline in MADRS total score. At a post-OL Baseline visit, responders relative to OL Baseline are defined as those who show a 50% or more reduction (ie, improvement) from OL Baseline. Remitters at any visit are defined as a subjects with a MADRS total score of ≤ 12. Frequencies and percentages of MADRS responders relative to both DB Baseline and OL Baseline, and frequencies and percentages of remitters will be summarized over time by analysis group.

15.4.3. Safety Analyses

All safety data will be summarized by analysis group based on the safety population. In addition, for a few selected safety assessments (ie, AEs, ECG, laboratory results, and vital signs), descriptive summary by analysis group will be provided based on the follow-up population, separately.

15.4.3.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Information on the format and version of the coding dictionary is provided in the DMP.

A treatment-emergent adverse event (TEAE) (hereafter referred to as AE) is an adverse event with onset data on or after the first day of the open-label treatment period through 7 days after study drug discontinuation (14 days for serious adverse events). The start of the open-label treatment period is defined as the first dose day for subjects previously randomized to placebo group and the OL Baseline visit date for subjects previously randomized to SEP-4199 CR groups.

The incidence of AEs, SAEs, and AEs leading to discontinuation due to AEs (or SAEs) will be summarized by analysis group (by presenting the number and percentage of subjects with one or more AEs in each category). The number and proportion of subjects with one or more AEs within a system organ class (SOC) and by preferred term (PT) will be presented by analysis group as well. The incidence of AEs (by preferred term, grouped by SOC) will also be summarized by severity, by the relationship to study medication, by the action taken regarding the study medication, as well as by the outcome. In addition, AEs will also be summarized by SOC, high-level term (HLT), and PT by presenting the number and percentage of subjects within each AE category.

The incidence of AESI, including but not limited to hyper-prolactinemia related AEs, will be summarized for overall and by gender as appropriate. For selected AESI, Kaplan-Meier curves will be plotted by analysis group for time to the earliest onsets. AEs associated with EPS will be summarized by analysis group.

Incidence of post-treatment adverse events (defined as an AE with a start date after the date of last dose of study drug through the last contact/visit in the follow-up period) will be summarized separately for subjects in the follow-up population.

15.4.3.2. Treatment-Emergent Mania

Treatment-emergent mania is defined as a YMRS score of ≥ 16 on any 2 consecutive OL visits (ie, including OL Baseline visit for subjects previously randomized to SEP380-4199 CR group or excluding the visit(s) with study day ≤ Day 1 for subjects previously randomized to placebo group) or at the final assessment in the OL treatment period, or any treatment-emergent AE of mania or hypomania. If a subject has reported no AE of mania or hypomania and has no YMRS assessment (including OL Baseline for subjects previously randomized to SEP380-4199 CR group or has no post-OL Baseline YMRS assessment for subjects previously randomized to placebo), incidence of treatment-emergent mania will be set to missing.

For YMRS total score, descriptive statistics will be provided for observed values and changes from DB Baseline and OL Baseline, respectively, by study visit and analysis group.

15.4.3.3. Clinical Laboratory Assessments

Descriptive statistics will be provided for observed values and changes from DB Baseline and OL Baseline, respectively, by study visit and analysis group for laboratory parameters measured on a continuous scale. Categorical results will be summarized by study visit and analysis group using frequency and percentage.

Results for glucose, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and lipid tests will be presented separately by fasting status, which includes fasting only, and overall (fasting, non-fasting, or unknown). Serum prolactin values will be summarized by analysis group and gender (male, female, and overall).

The normal reference ranges for laboratory tests will be used to determine whether the laboratory test value is below, within, or above the normal range. Shifts from DB Baseline and OL Baseline will be produced over time by analysis group to show the percentage of subjects with laboratory test values below, within, and above the normal range.

Number and percentage of subjects with potentially clinically significant (PCS) laboratory value for select parameters will be summarized by study visit and for assessment period (treatment-emergent) for each analysis group. Details of laboratory PCS criteria will be provided in the SAP.

15.4.3.4. ECGs

Standard 12-lead ECG parameters heart rate (HR), PR interval, RR interval, QT interval, QTcB and QTcF intervals, and QRS duration will be assessed. Results of each ECG parameter and their changes from DB Baseline and OL Baseline will be summarized by study visit and analysis group using descriptive statistics.

For overall ECG assessment, shift from DB Baseline and shift from OL Baseline will be summarized by study visit for each analysis group.

The number and percentage of subjects with elevated QTc intervals (> 450 msec for males, > 470 msec for females, > 450 msec, > 480 msec and > 500 msec for both males or females) and changes from Baseline in QTc intervals ≥ 30 msec, ≥ 30 msec but < 60 msec, and ≥ 60 msec will be summarized by study visit and overall by analysis group. For other ECG parameters, subjects will be classified as normal or abnormal (details will be provided in the SAP). Number and percentage of subjects with PCS ECG values will be summarized by study visit and for assessment period (treatment-emergent) for each analysis group. Details of ECG PCS criteria will be provided in the SAP.

15.4.3.5. Vital Signs

Descriptive statistics of the following parameters will be summarized by study visit for actual value, change from DB Baseline, and change from OL Baseline (including percent change of body weight) for each analysis group.

- Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate in supine and standing positions;
- Orthostatic changes in SBP, DBP, and pulse rate;
- BMI and body weight;

Number and percentage of subjects with weight increase of ≥ 3%, ≥ 5%, and ≥ 7% by visit will be summarized by study visit for each analysis group. Shifts from DB Baseline and shifts from OL Baseline over time for weight status categories (Underweight/Normal, Overweight, Obese) will be summarized by analysis group to show the number and percentage of subjects that fall into categories. Number and percentage of subjects with PCS vital signs values will be summarized by study visit and for assessment period (treatment-emergent) for each analysis group. Number and percentage of subjects with orthostatic hypotension and/or orthostatic tachycardia will be summarized similarly. Details of vital signs PCS criteria will be provided in the SAP.

15.4.3.6. Movement Disorder Measures

Descriptive statistics for actual value, change from DB Baseline, and change from OL Baseline in BARS total score, BARS global clinical assessment of akathisia score, AIMS total score, and SAS 10-item mean score will be presented by study visit and analysis group.

Shifts from DB Baseline and shift from OL Baseline in BARS global clinical assessment of Akathisia responses and AIMS global severity scores (classified as ‘worsened’, ‘unchanged’, or ‘improved’), AIMS total score and SAS 10-item mean score (classified as ‘abnormal’, ’normal’) will be summarized by study visit and analysis group. Details for definition of these classifications will be provided in the SAP.

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

The number and percentage of subjects with suicidal ideation, suicidal behavior, emergence or worsening of suicidal ideation or suicidal behavior will be summarized by analysis group for the open-label extension treatment period.

15.4.3.8. Physician's Withdrawal Checklist (PWC)

The PWC related summary will be based on the follow-up population. The PWC score will be summarized by presenting descriptive statistics of observed values and changes from Visit 14E (Month 12/EOT) by analysis group. Numbers and percentages of subjects with any new symptom or worsened old symptom for any PWC score or each individual symptom score will be provided by analysis group as well.

15.4.4. Pharmacokinetic and Pharmacodynamic Analysis

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.

15.4.5. Interim Analysis

No interim analysis is planned.

15.4.6. Treatment of Missing Data

Details for data handling rules of missing data will be provided in the SAP.

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

16.1. Data Collection/Electronic Data Capture (EDC)

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

16.2. Computerized Systems Used for Source Data

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

Table 6: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Informed consent	A
Informed consent for duplicate subject check	G
Inclusion/Exclusion Criteria Review	A
Dispense Study Drug	B
Administer Study Drug	A
Study Drug Accountability	A/B
Demographics	A
Physical Examination	A
Neurological Examination	A
Prior/Concomitant Medications	A
Vital Sign Measurements	A
Weight	A
Waist Circumference	A
Adverse Event Monitoring	A
12-Lead Electrocardiogram (ECG)	E
Serum Chemistry, Hematology, and Urinalysis	D
Serum Prolactin	D
Blood sample for aramisulpride and esamisulpride PK and Plasma Prolactin	F
Hemoglobin A1c (HbA1c)	D
Lipid Panel	D
Serum Insulin	D
High Sensitivity C-reactive Protein (hs-CRP)	D

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

Protocol Step	Computerized System Type or Description
Thyroid Panel	D
Urine β-hCG (Female Subjects of child-bearing potential)	A
Rapid Urine Drug Test	A
Young Mania Rating Scale (YMRS)	C
Columbia-Suicide Severity Rating Scale (C-SSRS)	C
Abnormal Involuntary Movement Scale (AIMS)	C
Barnes Akathisia Rating Scale (BARS)	C
Modified Simpson-Angus Scale (SAS)	C
Physician Withdrawal Checklist (PWC)	C
Montgomery-Asberg Depression Rating Scale (MADRS)	C
Clinical Global Impression – Bipolar Version-Severity of Illness (CGI-BP-S)	C
Hamilton Anxiety Rating Scale (HAM-A)	C
Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR16)	C
Sheehan Disability Scale (SDS)	C
EuroQoL - 5 Dimensions – 5 Levels (EQ-5D-5L)	C
Snaith-Hamilton Pleasure Scale (SHAPS)	C
Statistical analysis	SAS® software, version 9.4 or higher

Abbreviations: ASCII = American Standard Code for Information Interchange; EDC = electronic data capture; eCOA = electronic clinical outcome assessments; IXRS = interactive web response system; LIMS = laboratory information management system; PK = pharmacokinetic(s).
A = EDC (Rave EDC); B = IXRS; C = eCOA; D = Central Lab; E = ECG central vendor; F = LIMS/ASCII; G = duplicate subject database.

16.3. Study Monitoring

This study will be monitored using a risk-based approach from initiation to completion by the Sponsor or its representative. Monitoring will include central review, personal visits, and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with ICH GCP. On site review will be conducted to ensure source documents and other trial records are accurate and complete and, where applicable, consistent with eCRF entries.

16.4. Audits

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

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of center facilities (eg, pharmacy, drug

storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center standard operating procedures (SOPs), protocol, ICH GCP, and local regulations. The PI or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the IEC. Should the PI or appropriate designee be notified of a regulatory inspection involving this study, they should notify the Sponsor immediately.

16.5. Study Documentation

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

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

16.6. Clinical Laboratory Certification and Normal Values

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

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

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

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

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

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

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

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

17.2. Institutional Review Board/Independent Ethics Committee

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

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

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

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

17.3. Informed Consent

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

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

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

17.4. Subject Privacy

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

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

17.5. Protocol Amendments and Emergency Deviations

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

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

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years (or at least 25 years in the European Union [EU]) from time of completion of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

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

17.8. Financial Disclosure

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

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

17.9. Publication Policy

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

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

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

17.10. Compensation

If subjects have any adverse event or injury directly resulting from the study medications or procedures, the Sponsor will appropriately compensate them in accordance with applicable regulatory requirements.

18. REFERENCES

Abbas AI, Hedlund PB, Huang XP, Huang X-P, Tran TB Meltzer HY, Roth BL. Amisulpride is a potent 5-HT_7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology (Berl). 2009;205:119-28.

Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.

Barnes TRE. The Barnes Akathisia Rating Scale – Revisited. J Psychopharmacology. 2003;17(4):365-70.

Guy W. EDCEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76-338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976:534-7.

Hopkins SC, Wilkinson S, Corriveau TJ, Nishikawa H, Nakamichi K, Loebel A, et al. Discovery of Nonracemic Amisulpride to Maximize Benefit/Risk of 5-HT_7 and D_2 Receptor Antagonism for the Treatment of Mood Disorders. Clin Pharmacol Ther, 2021: Sep;110(3):808-815.

Huhn M, Nikolakopoulou A, Schneier-Thomas J, Krause M, Samara M, Peter N, et. al. Comparative efficacy and tolerability of 32 oral antipsychotics for acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019 Sep 14;394(10202):939-951.

Kemp DE. Managing the side effects associated with commonly used treatments for bipolar depression. J Affect Disord. 2014 Dec;169 Suppl 1:S34-44.

Lecrubier Y, Boyer P, Turkanski S, Rein W, Amisulpride Study Group. Amisulpride versus imipramine and placebo in dysthymia and major depression. J Affect Disord. 1997;43:95-103.

Montgomery, 2002. Dopaminergic deficit and the role of amisulpride in the treatment of mood disorders. International Clinical Psychopharmacology. 2002;17 (suppl 4): S9-S17.

Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. Hospital and Community Psychiatry. 1988;39:1172-7.

Schooler NR, Chengappa KNR. Adverse effects measures. In: Handbook of Psychiatric Measures. Washington, D.C.: American Psychiatric Association, 2000:151-68.

Solian SMPC, 23 Mar 2021.

Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavia. Suppl 1970;212S:11-9.

Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of the hedonic tone: The Snaith-Hamilton Pleasure Scale. B J Psychiatry. 1995;167(1):99-103.

19. INVESTIGATOR APPROVAL

I have read the protocol, SEP380-303, Version 2.02, "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)", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and/or Sumitomo Pharma Co., Ltd. (SMP) and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

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

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

2. Subject Restrictions and Instructions

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

3. Reporting

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

4. Data Standardization

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

21. APPENDIX II. CLINICAL LABORATORY TESTS

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)

Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC - Total Count, WBC Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red Cell Distribution Width (RDW)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate, Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Creatine Phosphokinase (CPK), Gamma-Glutamyl Transferase (GGT), Glucose, Lactate Dehydrogenase (LDH), Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid

URINALYSIS: Color, Clarity/Appearance, Specific Gravity, Bilirubin, Blood, Glucose, Ketones, Leukocyte esterase, Nitrites, pH, Protein, Urobilinogen, Microscopic examination

LIPID PANEL: Total Cholesterol, Low Density Lipoprotein (LDL)-Cholesterol, High Density Lipoprotein (HDL)-Cholesterol, Triglycerides

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

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

RENAL FUNCTIONING: Creatinine clearance (Calculated GFR)

OTHER TESTS: Serum Pregnancy (β-hCG) (female subjects of childbearing potential only), Urine Pregnancy Test (female subjects of childbearing potential only), HbA1c, Glucose, Serum Insulin, hs C-reactive Protein (CRP), Serum Prolactin

The Investigator listed on the Form FDA 1572 (MD or DO) (or Sub-Investigator MD or DO as described on the delegation log) will review laboratory reports and initial and date on all pages, or other acceptable documentation process approved by the Sponsor. Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

22. APPENDIX III. BLOOD SAMPLE COLLECTION AND HANDLING GUIDELINES FOR PHARMACOKINETIC AND PLASMA PROLACTIN ASSESSMENTS

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

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

Visit No.	Time	Aramisulpride and Esamisulpride PK and Plasma Prolactin Blood Sample Collection Times:
1E	Baseline (Day -1)	Carried over from 6-week double-blind placebo-controlled lead-in study of SEP-4199 CR
2E	Week 2 (± 2 days)	Postdose*
4E	Month 2 (± 5 days)	Postdose*
6E	Month 4 (± 5 days)	Postdose*
8E	Month 6 (± 5 days)	Postdose*
10E	Month 8 (± 5 days)	Postdose*
12E	Month 10 (± 5 days)	Postdose*
14E	Month 12 (+ 5 days)	Postdose*
15E	7 ± 2 days after last dose	Follow-up**

* Sample will be collected after dosing is given on that day. Actual date and time will be recorded.
** Actual date and time will be recorded.

COLLECTION REQUIREMENTS:

Collect 4 mL blood sample into a K_2EDTA (ethylenediaminetetraacetic acid) treated Vacutainer® (or equivalent) tube at each time point. Invert gently 8 to 10 times to mix well. Keep the blood collection tube on wet ice prior to centrifugation, and centrifuge for 10 minutes at approximately x 1500 g to isolate plasma within 30 minutes of blood collection. To ensure a more homogenous sample, all plasma samples should first be transferred to 1 tube and mixed well (by repeatedly aspirating and dispensing the sample into the storage tube). Split the sample with approximately equal volume into 2 polypropylene tubes, and label as Set-1 and Set-2. Store plasma tubes at approximately -20°C or lower freezer within 1 hour until shipping to the bioanalytical lab. The date and time of blood collection must be recorded.

All samples will be shipped with dry ice protection. Set-1 samples will be shipped to the Bioanalytical Lab for aramisulpride and esamisulpride concentration measurements and Set-2 samples will be shipped to another lab for prolactin concentration measurement.

23. APPENDIX IV. PROHIBITED DRUGS KNOWN TO PROLONG THE QT INTERVAL

Generic Name	Trade Name
Amiodarone	Cordarone, Pacerone
Azithromycin	Zithromax
Arsenic trioxide	Trisenox
Bepridil	Vascor
Chlorpromazine	Thorazine
Ciprofloxacin	Cetraxal, Cipro XR, Ciloxan
Cisapride	Propulsid
Clarithromycin	Biaxin
Disopyramide	Norpace
Dofetilide	Tikosyn
Dolasetron Mesylate	Anzamet
Domperidone	Motilium
Dronedarone	Multaq
Droperidol	Inapsine
Erythromycin	E.E.S., Erythrocin
Flecainide	Tambocor
Fluconazole	Diflucan
Gatifloxacin	Tequin
Halofantrine	Halfan
Haloperidol	Haldol
Ibutilide	Corvert
Levofloxacin	Levaquin
Levomethadyl	Orlaam
Mefloquine	Larium
Mesoridazine	Serentil
Methadone	Dolophine, Methadose
Moxifloxacin	Avelox
Ondansetron	Zofran, Zuplenz
Pentamidine	NebuPent
Pentamidine	Pentam
Pimozide	Orap
Probucol	Lorelco
Procainamide	Procan, Pronestyl
Quinidine	Cardioquin, Quiniglute
Sotalol	Betapace
Sparfloxacin	Zagam
Tacrolimus	Prograf
Thioridazine	Mellaril