SEP-4199 CR

Clinical Study Protocol SEP380-301

A Multi-region, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating 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. 2021-002126-24

Version 3.00

Incorporates Amendment 2.00

Incorporates Amendment 1.00

Incorporates Non-substantial Amendment 1.00

06 December 2022

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 Multi-region, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating 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

Phase of Development: 3

Study Objectives:

The objective of Study SEP380-301 is to evaluate the efficacy, safety, and tolerability of SEP-4199 CR formulation given as monotherapy at fixed doses of 200 mg/day and 400 mg/day compared with placebo in the treatment of subjects with major depressive episode associated with bipolar I disorder (bipolar I depression).

Primary Efficacy:

Evaluate the efficacy of SEP-4199 CR in the reduction of depression symptoms, as measured using the Montgomery-Asberg Depression Rating Scale (MADRS).

Secondary Efficacy:

Evaluate the efficacy of SEP-4199 CR in global improvement of bipolar depression severity, as measured using the Clinical Global Impression-Bipolar Version-Severity of Illness, Depression scale (CGI-BP-S depression).

Additional Efficacy:

- Assess the proportion of subjects with treatment response, defined as ≥ 50% reduction in MADRS total score.
- Assess the proportion of subjects with depression symptom remission, defined as a MADRS total score ≤ 12.
- Assess the effect of treatment on the core symptoms of depression, as measured using the MADRS-6 subscale, defined as summation of items 1, 2, 3, 7, 8, and 9.
- Assess the effect of treatment in the reduction of anxiety symptoms, as measured using the Hamilton Anxiety Rating Scale (HAM-A).
- Assess the effect of treatment on subject self-rated depression symptom severity, as measured by the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR16).
- Assess the effect of treatment on functional impairment, as measured by the Sheehan Disability Scale (SDS).
- Assess the effect of treatment on quality of life, as measured by the EuroQol - 5 Dimension - 5 Level (EQ-5D-5L).
- Assess the effect of treatment on anhedonia, as measured by the Snaith-Hamilton Pleasure Scale (SHAPS).

Safety:

- Determine the incidence of adverse events (AEs), discontinuation due to AEs, serious AEs (SAEs), and adverse events of special interest (AESI).
- Evaluate safety and tolerability using physical examinations, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory tests, prolactin levels, metabolic parameters, body weight, and body mass index (BMI).
- Monitor for akathisia and extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BARS), and Modified Simpson-Angus Scale (SAS).
- Monitor for treatment-emergent mania or hypomania, defined as a Young Mania Rating Scale (YMRS) score of ≥ 16 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania.
- Monitor for suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Evaluate potential withdrawal symptoms using the Physician's Withdrawal Checklist (PWC).

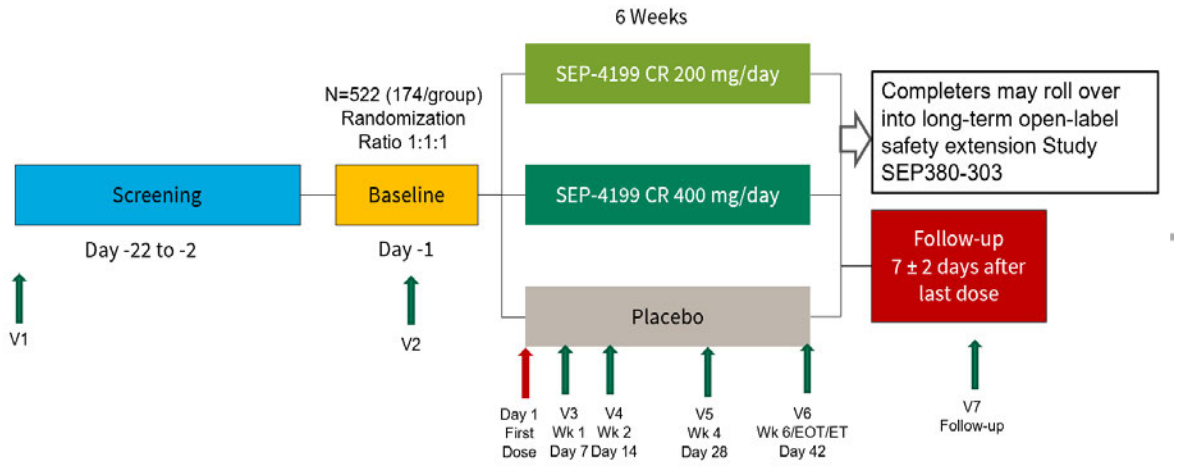
Pharmacokinetics and Pharmacodynamics:

- Evaluate the therapeutic plasma concentration range of SEP-4199 CR taken as 200 mg/day and 400 mg/day for treatment of major depressive episode associated with bipolar I disorder.
- Perform population pharmacokinetic (Pop-PK) analysis using plasma concentrations of SEP-4199 CR 200 mg/day and 400 mg/day.
- Evaluate the relationship between SEP-4199 PK and plasma prolactin levels for SEP-4199 CR 200 mg/day and 400 mg/day.
- Explore the exposure-response relationship of SEP-4199 CR 200 mg/day and 400 mg/day and symptoms as measured by MADRS using population pharmacokinetic (PK)/pharmacodynamics (PD) methods.

Study Design: SEP380-301 is a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety, and tolerability of treatment with SEP-4199 CR at fixed doses of 200 mg/day or 400 mg/day compared with placebo for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression). The study is projected to randomize approximately 522 subjects in North America, Latin America, Japan, and Europe to SEP-4199 CR 200 mg/day, SEP-4199 CR 400 mg/day, and placebo treatment groups in a 1:1:1 ratio, resulting in approximately 174 subjects/group.

The study will consist of a Screening Period (up to 21 days), a 6-week double-blind Treatment Period (42 days), and a Follow-up Period (7 [± 2] days after the last study drug dose), as shown in the Study Schematic. If necessary, subjects may return to the clinic at any time for an unscheduled visit. Subjects who complete the Treatment Period are eligible to enroll directly into a long-term open-label safety extension study (SEP380-303) of SEP-4199 CR. Those subjects who prematurely discontinue or who complete the Treatment Period and choose not to enroll in the long-term open-label safety extension study will have a follow-up safety visit 7 (± 2) days after their last dose of double-blind study drug.

Study Schematic



Abbreviations: CR = controlled release; EOT = end of treatment; ET = early termination; V = visit; Wk = week
Note: Subjects who do not enroll in the long-term open-label safety extension study will have Visit 7.

Screening Period (Visit 1, Day -22 to -2)

Subjects will be evaluated at the Screening Visit (Visit 1) to determine their eligibility to enroll in the study. This visit should be scheduled as an early morning appointment, if possible, due to the recommendation that subjects fast prior to blood sample collection for clinical laboratory tests. Subjects should be advised to obtain and bring medical records as well as any current medications that they are taking. A highly reliable informant (who has had close contact with the subject and is approved by the Sponsor Eligibility Committee) should be identified to provide collateral information on the subject's psychiatric and treatment history.

Informed consent will be obtained from each subject before any study procedures are performed for this study. Medical, psychiatric, family (eg, biological mother, father, siblings, children) psychiatric and medical, and medication histories will be obtained. Medical history should include information about prior coronavirus disease 2019 (COVID-19) vaccination, infection, and illness, if any. Information supporting a diagnosis of Bipolar I disorder with at least one prior manic episode or manic episode with mixed features must be obtained from additional sources to confirm the Screening evaluation.

The subject's eligibility assessments will be reviewed by the Sponsor Eligibility Committee, which consists of the contract research organization's (CRO) medical team along with the Sponsor and sponsor designees based on protocol-specified inclusion and exclusion criteria (see Section 26, Appendix VII for details). The Sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility. In the event the Sponsor Eligibility Committee and Investigator do not agree on a subject's eligibility, then the subject will not be approved to proceed to the Baseline Visit (Visit 2).

Subjects will discontinue and wash out prior or concomitant medications, as applicable, prior to Baseline. Psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) are to be discontinued as tolerated and clinically appropriate at least 3 days or 5 half-lives (whichever is longer) prior to Baseline.

Hospitalization during the Screening Period will not be allowed, except

- where required by local regulations, or
- when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms.

Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization. In such cases, a maximum of 7 days' hospitalization during washout of prior medications in the Screening Period and a maximum of 7 days' hospitalization during Week 1 of study medication dosing will be allowed. If an extension is required, medical justification must be provided to the Medical Monitor, and the Medical Monitor, following Sponsor review, must approve the request to extend the duration of hospitalization.

To determine subject eligibility, abnormal Screening clinical laboratory tests may only be repeated after discussion with the Medical Monitor.

To determine subject eligibility, the Screening ECG may be repeated in the event of technical difficulty or error associated with the first ECG or if clinically indicated. Subjects should rest supine for at least 10 minutes prior to all ECGs.

All Screening assessments should be completed in sufficient time for Site and CRO/Sponsor to receive and review results prior to the Baseline Visit (Visit 2). If necessary, to ensure receipt and review of all Screening information, an extension of the Screening Period by up to 7 days may be allowed, with prior approval from the Medical Monitor.

Subjects who meet all inclusion criteria and no exclusion criteria after full evaluation of Screening data may proceed to the Baseline Visit (Visit 2) after receiving approval from the Sponsor Eligibility Committee.

Baseline Visit (Visit 2, Day -1)

Subjects who meet eligibility criteria during the Screening Period will return to the study site on Day -1 for confirmation of Screening evaluations as well as completion of pre-dose assessments. Subjects who continue to meet all inclusion criteria and no exclusion criteria at Baseline will be randomized and dispensed study drug at Day -1.

Double-blind Treatment Period (Visits 3-6, Days 1 to 42)

Subjects will self-administer the study drug on an outpatient basis once daily with or without food beginning on the morning of Day 1 (the day after the Baseline Visit [Visit 2]) and continue for 6 weeks. Subjects will be instructed to administer study drug as a single oral dose at approximately the same time each morning. Subsequent clinic visits should be scheduled to begin no later than 6 hours post-dose, if possible. The last dose of study drug will be self-administered by the subject at home on the morning of Visit 6 (Day 42).

During the Treatment Period, subjects will have clinic visits as follows: Visit 3 (Day 7), Visit 4 (Day 14), and Visit 5 (Day 28). Telephone calls to ascertain AEs and concomitant medications will be scheduled on Days 21 and 35. In order to facilitate scheduling of clinic visits and telephone calls, a window of ± 2 days will be allowed for each clinic visit and telephone call.

End of Treatment (EOT)/Early Termination (ET) (Visit 6, Day 42 [± 2 days])

Subjects will have a clinic visit at Visit 6 (Day 42) for efficacy and safety assessments. Subjects who complete the 6-week double-blind Treatment Period will be considered study completers, and may be eligible to enroll directly into a long-term open-label safety extension study of SEP-4199 CR (SEP380-303).

Subjects who prematurely discontinue the study will undergo an Early Termination (ET) Visit at the time of discontinuation. The ET Visit will include all efficacy and safety assessments scheduled for Visit 6 (Day 42). Prematurely discontinued subjects will not be eligible for the long-term open-label safety extension study.

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

All subjects who received at least one dose of study drug and who do not enroll in the subsequent open-label safety extension study will have a Follow-up Visit for safety and tolerability assessments 7 (± 2) days after their last dose of double-blind study drug. Assessment of potential withdrawal effects will also be made during the Follow-up Period. During the Follow-up Period, completed subjects who do not continue into an open-label safety extension study will not be allowed to initiate treatment with a psychotropic medication until after completion of the Follow-up Visit. In the event that the severity of major depressive episode (MDE) symptoms at the Week 6 EOT/ET visit is judged to present a safety risk to complying with this requirement, the subject should be discontinued from the study and managed as clinically appropriate by the Investigator.

Diagnostic and Symptom Severity Scales to Inform Subject Eligibility

The Lifetime Illness Characteristics Questionnaire will be administered as an initial Screening assessment at Visit 1, prior to other Screening assessments. Subject responses are used to calculate a Bipolarity Index Score. A score ≥ 50 is associated with a high likelihood of a diagnosis of bipolar disorder.

Diagnosis of bipolar I disorder, current episode depressed, will be based on the Structured Clinical Interview for DSM-5-Clinical Trials version (SCID-5-CT). Moderate-to-severe depression symptoms will be established with a score ≥ 22 on both the MADRS and Montgomery-Asberg Depression Rating Scale, self-rating version (MADRS-S), and with a CGI-BP-S depression score ≥ 4. Absence of mania will be established with a YMRS score ≤ 12.

Details of these diagnostic and symptom severity scales are provided in Section 11.3.

Efficacy Assessments

Efficacy assessments include the clinician-rated MADRS, CGI-BP-S, and HAM-A; and subject self-reported measures of depression (QIDS-SR16), functional impairment (SDS), quality of life (EQ-5D-5L), and anhedonia (SHAPS). Details of these efficacy assessments are provided in Section 11.4 and in Table 2 (Schedule of Assessments).

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, BMI, and waist circumference will also be recorded. Adverse events of special interest (AESI), including but not limited to hyperprolactinemia-related AEs, will be evaluated. Movement disorders will be assessed by AIMS, BARS, and modified SAS; and AEs associated with EPS will be summarized. 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 11.5 and in Table 2 (Schedule of Assessments).

Pharmacokinetic Assessments

Blood samples will be collected for pop-PK at Baseline (Visit 2), Visit 4 (Day 14), Visit 6 (Day 42), and Visit 7 (Follow-up). These samples, together with a sample collected at Screening (Visit 1), will also be measured for plasma prolactin levels.

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 electronic case report form (eCRF) (Visit 4 [Day 14] and Visit 6 [Day 42] only).

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

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): 522 (174/group)

Main Diagnosis and Criteria for Subject Inclusion:

Primary Inclusion Criteria (not all inclusive):

1. Subject provides written informed consent and is willing and able to comply with the protocol in the opinion of the Investigator.
2. Subject or legally acceptable representative must possess an educational level and degree of understanding of English or the local language that enables them to communicate suitably with the Investigator and the study coordinator.
3. Subject is 18 to 65 years of age, inclusive, at the time of informed consent.
4. Subject meets DSM-5 criteria, based on the SCID-5-CT, for bipolar I disorder, current episode depressed with or without rapid cycling disease course (≥ 4 episodes of mood disturbance but < 8 episodes in the previous 12 months) with or without psychotic features.
5. Subject has a lifetime history of at least 1 manic episode or manic episode with mixed features corroborated by at least one of the following: medical records, documented correspondence with a treating psychiatrist or mental healthcare provider/staff, or information from a reliable informant who is familiar with the subject's psychiatric history. The adequacy of the information will be assessed by the Sponsor Eligibility Committee.
6. Attempts should be made to obtain supporting information regarding the subject's current major depressive episode from additional sources. This may include relevant medical records and/or documented correspondence with a treating psychiatrist or mental healthcare provider/staff if the subject has been evaluated during the current MDD episode, or information from a reliable informant who is familiar with the subject's recent psychiatric history.
7. Subject's current major depressive episode is ≥ 4 weeks and less than 12 months in duration at Screening.
8. Subject has a MADRS-S total score ≥ 22 at Screening.
9. Subject has a MADRS total score ≥ 22 at both Screening and Baseline.
10. Subject has a CGI-BP-S depression score ≥ 4 at both Screening and Baseline.
11. Subject has a YMRS total score ≤ 12 at both Screening and Baseline.
12. Subjects meets an additional inclusion criterion at Baseline that will remain blinded to clinical site Investigators and staff.

Primary Exclusion Criteria (not all inclusive):

1. Subject currently has any DSM-5 defined psychiatric diagnosis other than bipolar I disorder that was the primary focus of treatment or is currently being treated with concomitant medication.
2. Subject has a lifetime history of, or symptoms consistent with, schizophrenia, schizoaffective disorder, or a major psychiatric diagnosis other than bipolar I disorder that is judged to pose risk to the study scientific objectives based on the judgement of the Investigator or the Sponsor

Eligibility Committee. A lifetime history of anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD) are not exclusionary if the disorder does not meet Exclusion Criterion 1. (**Note:** Subjects with a previous diagnosis of major depressive disorder or bipolar II disorder that was subsequently changed to bipolar I disorder are allowed.)

3. Subject has a history within the past 12 months prior to Screening of substance use disorder.
4. Subject has confirmed or suspected borderline personality disorder.
5. Subject demonstrates a decrease (improvement) of ≥ 25% in MADRS total score from Screening to Baseline.
6. Subject is considered by the Investigator to be at imminent risk of suicide or injury to self or others, or has a score ≥ 4 on MADRS item 10 (suicidal ideation) 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 the Screening Visit (in the past 3 months [90 days]) or at Baseline.
7. Subject has received any psychotropic medication or herbal supplement within 3 days or 5 half-lives (whichever is longer) prior to Baseline or anticipates the need for psychotropic medications or herbal supplements during participation in this study, with the exception of the medications specified in Protocol Section 10.3. The following treatments have additional restrictions as specified below:
   a. Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to Baseline.
   b. Fluoxetine, and olanzapine/fluoxetine combination must be discontinued at least 28 days prior to Baseline.
   c. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to Baseline. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation.
   d. Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to Baseline.
   e. Subjects with a history of treatment with ketamine, esketamine, arketamine, or psychedelic therapies (eg, psilocybin, methylenedioxymethamphetamine [MDMA]) for MDD or any psychedelic treatment.
   f. Electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) within 90 days prior to Baseline.
   g. Subjects with a history of treatment with vagus nerve stimulation (VNS) or deep brain stimulation (DBS) are excluded from study participation.
8. Subject initiated a new psychotherapeutic intervention (eg, psychotherapy) focused on treatment of bipolar I depression within the past 12 weeks prior to Screening. (**Note:** Subjects who have participated in ongoing psychotherapy treatment for at least 12 weeks prior to Screening will be permitted to continue this treatment during the study.)
9. Subject has a history of non-response to an adequate (6-week) trial of 3 or more antidepressants (with or without mood stabilizers) during the current major depressive episode.
10. Subject was hospitalized during the Screening Period without explicit approval by the Medical Monitor. (**Note:** Hospitalization during the Screening Period will not be allowed, except where required by local regulations, or when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms. Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization.)

11. Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that would pose a risk to the subject or that might confound the results of the study. (**Note:** Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to subject or study results. In cases in which the impact of the condition upon risk to subject or study results is unclear, the Medical Monitor should be consulted.)
    a. Hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular (including unstable hypertension), hepatic, neurologic, or allergic disease that is clinically significant or unstable (except for seasonal allergies at time of dosing). (**Note**: Any subject with a known cardiovascular disease or condition, including hypertension, [even if under control and considered stable] must be discussed with the Medical Monitor before being randomized in the study.)
    b. Chronic organic disease of the CNS such as tumors, inflammation, active (or history of) seizure disorder, vascular disorder, Parkinson's disease, Alzheimer's disease or other forms of dementia, myasthenia gravis, or other degenerative processes. Subject has history of intellectual disability or persistent neurological symptoms attributable to serious head injury. (**Note**: Past history of febrile seizure is not exclusionary.)
    c. Evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation. Subjects who test positive for hepatitis C antibody at Screening and have a positive or indeterminate confirmatory test for hepatitis C are excluded. Subjects who test positive for hepatitis B surface antigen at Screening are excluded.
    d. History of any cardiovascular disorder/condition known to increase the possibility of QT prolongation, history of additional risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome or Brugada Syndrome) or cardiac conduction disorders, or requires treatment with an antiarrhythmic medication.
    e. History of neuroleptic malignant syndrome (NMS).
    f. History of malignancy < 5 years prior to the Screening Visit, except for adequately treated basal cell carcinoma or squamous cell skin cancer or in situ cervical cancer. Subjects with lifetime history of pituitary tumors, including pituitary adenoma, of any duration are excluded.
    g. History of a condition (including history of malabsorption) or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, bowel resection) that could interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH.
    h. Known history of human immunodeficiency virus (HIV) seropositivity.
    i. Type 1 diabetes or insulin-dependent type 2 diabetes.
12. Subject with a supine systolic blood pressure (SBP) ≥ 150 millimeters of mercury (mmHg) and/or supine diastolic blood pressure (DBP) ≥ 95 at Screening or Baseline. A repeat blood pressure measurement is allowed once during the Screening Period and once at Baseline. The repeat measurements can be used to determine eligibility. The repeat blood pressure measurement at Screening can be conducted on a different day within the Screening Period, if needed.
13. Subject has a BMI ≥ 40 or < 18 kg/m^2 at Screening.

A complete listing of study entry criteria is provided in Section 8.

Investigational Product, Dosage and Mode of Administration:

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

Double-blind treatment will be self-administered by the subject once daily for 6 weeks.

Reference Therapy, Dosage and Mode of Administration:

Placebo will be supplied as tablets matching the active treatment.

Placebo 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.

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 eCRF.

Treatment with all prior psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) and herbal supplements must be discontinued as tolerated and clinically appropriate at least 3 days or 5 half-lives (whichever is longer) prior to Baseline. Subjects treated with MAOIs, fluoxetine, or olanzapine/fluoxetine combination must discontinue these medications at least 28 days prior to randomization. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to Baseline. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation. Depot neuroleptics must have been discontinued at least 30 days or one treatment cycle (whichever is longer) prior to Baseline. Subjects who, in the opinion of the Investigator, cannot safely discontinue prior psychotropic medications, are not eligible for the study and will be screen failed.

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during Screening and after Baseline if the dose and regimen have been stable (± 25%) for at least 30 days prior to Screening. Medications for short-term (no more than 10 days) treatment of a medical condition are allowed provided that the medications do not prolong the QTc interval. Section 24, Appendix V provides a representative, but not exhaustive, list of medications that prolong the QT interval and are not allowed during the study.

Medications used to treat movement disorders should be tapered and discontinued prior to Baseline but may be reinstituted 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 during Screening and for Weeks 1-3 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 for any reason, and the use of dietary supplements or other complementary or alternative medications for treating depression during the trial is not permitted.

Further details are provided in Section 10.3.

Study Endpoints:

Primary Efficacy Endpoint:

- Change from Baseline to Week 6 in MADRS total score

Secondary Efficacy Endpoints:

- Change from Baseline to Week 6 in CGI-BP-S depression score

Additional Efficacy Endpoints:

- Change from Baseline in MADRS total score at Weeks 1, 2, and 4
- Change from Baseline in CGI-BP-S depression score at Weeks 1, 2, and 4
- The proportion of subjects with treatment response, defined as ≥ 50% reduction from Baseline in MADRS total score, at Week 6
- The proportion of subjects meeting criteria for remission, defined as MADRS total score ≤ 12, at Week 6
- Change from Baseline to Week 6 in the MADRS-6 core symptoms subscale
- Change from Baseline in HAM-A total score at Weeks 1, 2, 4, and 6
- Change from Baseline to Week 6 in the QIDS-SR16 score
- Change from Baseline to Week 6 in the SDS total score 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) at Week 6
- Change from Baseline to Week 6 in the EQ-5D-5L Index score and VAS score
- Change from Baseline to Week 6 in the SHAPS total score

Safety Endpoints:

- The incidence of overall AEs, discontinuation due to AEs, and SAEs
- The incidence of hyperprolactinemia-related AESI by sex and overall
- Clinical laboratory evaluations (serum chemistry, hematology, thyroid panel, and urinalysis)
- Clinical evaluations (vital signs including orthostatic effects, and 12-lead ECGs)
- Change and percent change from Baseline to Week 6 in body weight (kg)
- Change from Baseline to Week 6 in BMI (kg/m^2)
- Changes from Baseline in metabolic parameters, including glucose, hemoglobin A1c (HbA1c), insulin, Homeostatic Model Assessment for Insulin (HOMA-IR), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides at Week 6.
- Incidence of treatment-emergent mania, defined as a YMRS total score ≥ 16 at two consecutive visits or at final visit, or an AE of hypomania or mania
- Mean changes from Baseline and the proportion of subjects with worsening on the movement disorders scales: AIMS, BARS, and modified SAS at Week 6

- Frequency and severity of suicidal ideation and suicidal behavior as assessed by the C-SSRS
- Occurrence of potential symptoms of withdrawal from SEP-4199 CR measured by change from Week 6 in the PWC total score at the safety Follow-up Visit

Pharmacokinetic and Pharmacodynamic Endpoints:

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

Statistical Methods:

The primary analysis population for the efficacy analysis will be the Intent-to-Treat (ITT) population. The ITT population will include all randomized subjects who receive at least one dose of study medication and have at least one post-Baseline assessment in any efficacy variable.

Unless otherwise specified, the safety data analysis will be based on the Safety population. The Safety population will include all randomized subjects who receive at least one dose of study medication.

Estimand of Primary Interest

Population of Interest	Adults who meet inclusion/exclusion criteria (major depressive episode associated with bipolar I disorder and have moderate-to-severe symptoms of depression as demonstrated by a MADRS total score ≥ 22 and CGI-BP-S depression score ≥ 4 at Screening and Baseline) and are in the ITT population.
Outcome Measure/ Endpoint	Change from Baseline in MADRS total score at Week 6
Treatment Condition of Interest	A hypothetical strategy is used to address intercurrent event, assuming that the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.
Intercurrent Event	Regardless of adherence to treatment (ie, discontinuation of assigned treatment)
Population Level Summary Measure	Treatment difference between SEP-4199 CR dose groups and placebo for mean change from Baseline in MADRS total score by using the mixed model for repeated measures (MMRM) per the randomized treatment based on the ITT population.

Primary Efficacy Endpoint Analyses

The primary efficacy analyses of the primary efficacy endpoint (the change from Baseline in MADRS total score at Week 6) will be performed using a likelihood-based MMRM model based on the ITT population. The response (dependent) variable is the change from Baseline in the MADRS total score assessed at Weeks 1, 2, 4, and 6. Specifically, the MMRM model includes fixed effects terms for treatment, visit (as a categorical variable), pooled country, Baseline MADRS total score, and treatment-by-visit interaction. Restricted maximum likelihood estimation method will be applied using an unstructured covariance model. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. The least squares (LS) mean treatment differences (each SEP-4199 CR dose minus placebo) of change from Baseline at Week 6, 2-sided 95% confidence intervals (CI), and the associated p-values will be calculated based on this model.

The model assumptions underlying the primary analysis will be assessed. Specifically, the normality and homoscedasticity assumptions underlying the primary MMRM model will be assessed graphically. Conditional studentized and scaled residuals will be plotted against the predicted values, respectively, and Q-Q (quantile-quantile) plots of these residuals versus the expected quantiles of the standard normal distribution will be presented to provide a graphical view of similarity and difference

in the two distributions. If the unstructured covariance model fails to converge, a more parsimonious model is likely necessary, but not necessarily correct. in this case, an MMRM based on structures more general than unstructured one, ie, separate unstructured matrices by treatment, will be checked. If there is evidence of deviations from the model assumption(s), the degree and nature of such deviation(s) will be explored to better understand the potential impact on interpretation of the primary efficacy analysis.

The primary efficacy analysis will be repeated for the Per Protocol (PP) population to examine the impact of protocol violation and deviations in a way that is less biased and to obtain a more interpretable result.

The primary efficacy endpoint will also be analyzed using an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) approach, as a supportive analysis. The model will include terms for treatment, pooled country, and Baseline MADRS total score as covariates.

To address early dropouts under the assumption of missing not at random (MNAR), a pattern-mixture model using a placebo-based multiple imputation method and a pattern mixture model using multiple imputations with penalties (ie, deflating the individually estimated treatment effect size by known factors) will be performed as sensitivity analyses to explore the robustness of the MMRM results for the primary analysis. In case of a deviation from the assumptions required for the primary analysis, to confirm the robustness of the primary analysis result, additional sensitivity analysis per permutation test will be performed: fit a large number of datasets based on a same MMRM for the primary analysis with randomly assigning pseudo-treatment group designations.

To support global regulatory decision-making, the consistency of treatment effects across regions (ie, North America, Latin America, Europe, Japan) will be assessed. Treatment effects and measures of their uncertainty for individual region, and treatment-by-region interaction will be evaluated for the primary efficacy endpoint. An MMRM model that includes fixed effects terms for treatment, visit (as a categorical variable), region, Baseline MADRS total score, treatment*visit interaction, treatment*region interaction, and treatment*visit*region interaction, will be performed using an unstructured covariance matrix. If p-value for treatment-by-region interaction at Week 6 is significant at level of 0.10, the nature of this significant interaction (quantitative vs qualitative) will be further evaluated using the Gail and Simon test (Gail 1985) and other interaction tests such as the Pan-Wolfe test (Pan 1997). Shrinkage analyses for treatment effect of regions, which are based on weighted averages of the overall effect estimate and the estimate using data from individual regions, will be performed. Shrinkage analyses for treatment effect of countries may be performed, as appropriate.

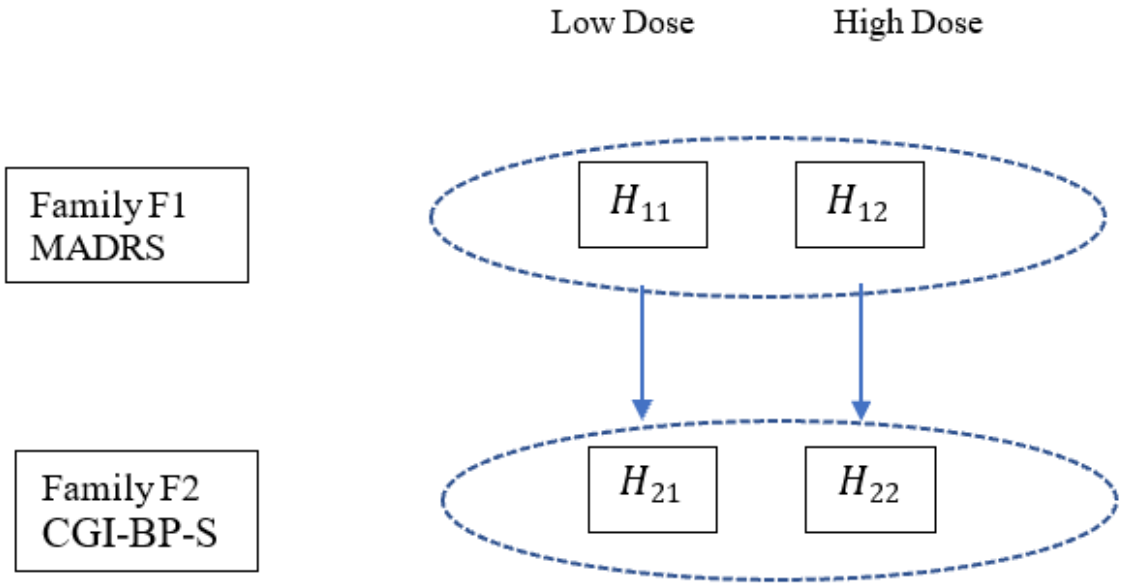
Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoint (change from Baseline in CGI-BP-S depression score at Week 6) will be analyzed with an MMRM model similar to the one used in the primary efficacy analysis (adjusted with the corresponding Baseline). The LS mean treatment differences (each SEP-4199 CR dose minus placebo) of change from Baseline at Week 6, their 2-sided 95% CIs, and the associated p-values will be calculated based on the model. Additional supportive and sensitivity analyses to the ones performed for the primary efficacy endpoint will be conducted for the secondary efficacy endpoint to address early dropouts or potential deviations from the model assumption(s).

Multiplicity Adjustment

The hypotheses associated with the primary and secondary variables for efficacy claim are grouped into 2 hierarchical families: Families 1 and 2, respectively. The enhanced mixture truncated Hochberg-based gatekeeping procedure with the logical relationships among the hypotheses (ie, H_{21} will be tested only if H_{11} is rejected; H_{22} will be tested only if H_{12} is rejected) will be applied to control the family-wise Type 1 error rate of 5% (two-sided) for the hypotheses in Families 1 and 2. The truncation parameter in Family 1, which is used to determine α propagation rule, is chosen as 0.5. The details for how to generate corresponding adjusted p-value for individual hypothesis based on

above multiplicity adjustment approach will be provided in the statistical analysis plan (SAP), and the rationale of choosing a truncation parameter is provided in Section 15.4.3.4.



Additional Efficacy Endpoint Analyses

MADRS-6 core symptoms subscale score and HAM-A total score will be analyzed with an MMRM model similar to the one used in the primary efficacy analysis adjusted with the corresponding Baseline. QIDS-SR16 total score, SDS total score and subscale scores, EQ-5D-5L related scores, and SHAPS total score will be analyzed with an ANCOVA model similar to the one used in the supportive ANCOVA analysis for the primary efficacy endpoint adjusted with the corresponding Baseline as covariate.

Categorical efficacy endpoints (ie, proportion of the responders and proportion of the remitters at Week 6) will be analyzed using a logistic regression model with treatment, region, and Baseline MADRS total score as covariates using a LOCF approach. Proportion of subjects meeting functional remission criteria per the SDS subscales (defined as SDS total score ≤ 6 and SDS subscale scores ≤ 2) will be analyzed using a similar logistic regression model with corresponding Baseline as covariate.

Safety Analyses:

A treatment-emergent adverse event (hereafter referred to as AE) is defined as an AE with a start date on or after the date of first dose through 7 days after study drug discontinuation (14 days for serious adverse events) for subjects who complete or discontinue this study but do not enter into the extension study, or through the last study day of the double-blind treatment period for subjects continuing into the extension study.

The number and percentage of subjects with AEs, discontinuation due to AEs, and SAEs will be summarized by treatment group. The incidence of AEs of special interest, including but not limited to hyperprolactinaemia-related AEs, will be summarized by treatment group for overall and by gender as appropriate. Incidence of post-treatment AEs (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.

Descriptive statistics (mean, median, etc) will be provided by visit and treatment group for observed values or changes from Baseline for safety variables (continuous). Categorical results (eg, urinalysis tests) will be summarized by study visit and treatment group using frequency and percentage. In addition, the change from Baseline at endpoint for selected laboratory parameters (eg, HbA1c, insulin, HOMA-IR, glucose, lipids parameters, prolactin) will be evaluated using a nonparametric rank ANCOVA analysis. For comparison versus placebo, stratified by region, the change from Baseline at endpoint and Baseline value will be ranked. A linear regression will be conducted by region, on the change from Baseline ranks and Baseline value rank as independent variable to produce regression residuals. Using the values of the residuals as scores, Mantel-Haenszel row mean score tests will be produced for each SEP-4199 CR dose group versus placebo after stratification by region.

An MMRM analysis will be performed to compare SEP-4199 CR dose groups with placebo for change from Baseline in YMRS score. The MMRM model includes fixed effects terms for treatment, visit (as a categorical variable), region, corresponding Baseline score, and treatment-by-visit interaction. An ANCOVA model using the LOCF approach will be conducted for change and percent change from Baseline in body weight (kg), changes from Baseline in BMI (kg/m^2), BARS total score, AIMS total score, and SAS 10-item mean score. The ANCOVA model will include terms for treatment, region, and corresponding Baseline value as covariate.

Treatment-emergent mania is defined as a YMRS score of ≥ 16 on any 2 consecutive post-Baseline visits or at the final assessment, or an AE of mania or hypomania. If a subject has no reported AE of mania or hypomania and has no post-Baseline assessment of YMRS, incidence of treatment-emergent mania will be set to missing. SEP-4199 CR will be compared to placebo in incidence of treatment-emergent mania in a logistic regression model including factors of treatment, region, and Baseline YMRS total score as covariate.

For the 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 treatment group for overall post-Baseline treatment period.

The PWC score will be summarized by presenting descriptive statistics of observed values and changes from Week 6 (EOT/ET) by treatment group for the follow-up period.

Sample Size: The sample size is estimated based on the primary efficacy endpoint, the change from Baseline in MADRS total score at Week 6. Based on the Phase 2 Study SEP380-201 results for both planned and post-hoc analyses of the primary endpoint, a common standard deviation (SD) of 10 and mean improvement of 3.5 (which resulted in an effect size 0.35) over placebo are assumed for both SEP-4199 CR 200 mg/day and 400 mg/day dose groups. With a randomization ratio of 1:1:1 for placebo, SEP-4199 CR 200 mg/day and 400 mg/day, a sample size of 165 subjects per treatment group will provide at least 80% conjunctive power to reject both null hypotheses of no difference between SEP-4199 CR doses and placebo and at least 85% power to reject each individual null hypothesis after multiplicity adjustment for two comparisons of the primary endpoint using the enhanced mixture truncated Hochberg gatekeeping procedure (truncation parameter 0.5, 2-sided Type I error of 0.05). An upward adjustment of approximately 5% is assumed to compensate for subjects who are randomized but have no post-Baseline efficacy assessment. Thus, a total sample of approximately 174 subjects per group (522 subjects in total) will be randomized. The sample size calculation is based Monte Carlo computer simulations.

Table 2: Schedule of Assessments

	Visit 1	Visit 2[a]	Visit 3	Visit 4	TC1[b]	Visit 5	TC2[b]	Visit 6[c]	Visit 7[d]
	Screening Washout[e]	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 EOT/ET	Follow-up
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 35 (± 2)	Day 42 (± 2)	7 (± 2) days after last dose
Obtain informed consent	X								
Obtain informed consent for duplicate subject check (where local regulations allow)	X								
Obtain informed consent for optional pharmacogenomic sampling, if applicable		X							
Lifetime Illness Characteristics Questionnaire[f]	X								
Montgomery-Asberg Depression Rating Scale, Self-rating version (MADRS-S)[f]	X								
Inclusion/Exclusion Criteria	X	X							
Duplicate Subject Check	X								
Pre-Baseline Eligibility Review[g]	X								
Demographics	X								
Medical History	X								
Psychiatric History[h]	X								
Family Psychiatric and Medical History	X								
Structured Clinical Interview for DSM-5-Clinical Trial Version (SCID-5-CT)[i]	X								
Physical Examination	X	X						X	X

Table 2: Schedule of Assessments (Continued)

	Visit 1	Visit 2[a]	Visit 3	Visit 4	TC1[b]	Visit 5	TC2[b]	Visit 6[c]	Visit 7[d]
	Screening Washout[e]	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 EOT/ET	Follow-up
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 35 (± 2)	Day 42 (± 2)	7 (± 2) days after last dose
Neurological Examination	X	X						X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X
Subject Eligibility Check[j]		X							
Randomization		X							
Dispense Study Drug		X	X	X		X			
Study Drug Accountability[k]			X	X		X		X	
Schedule Next Visit[l]	X	X	X	X		X		X	
EFFICACY ASSESSMENTS									
Montgomery-Asberg Depression Rating Scale (MADRS)[m]	X	X	X	X		X		X	
Hamilton Anxiety Rating Scale (HAM-A)[n]		X	X	X		X		X	
Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16)		X						X	
Sheehan Disability Scale (SDS)		X						X	
EuroQol - 5 Dimension - 5 Level (EQ-5D-5L)		X						X	
Snaith-Hamilton Pleasure Scale (SHAPS)		X						X	
Clinical Global Impression-Bipolar Version-Severity of Illness (CGI-BP-S)[o]	X	X	X	X		X		X	

Table 2: Schedule of Assessments (Continued)

	Visit 1	Visit 2[a]	Visit 3	Visit 4	TC1[b]	Visit 5	TC2[b]	Visit 6[c]	Visit 7[d]
	Screening Washout[e]	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 EOT/ET	Follow-up
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 35 (± 2)	Day 42 (± 2)	7 (± 2) days after last dose
SAFETY ASSESSMENTS									
Vital Sign Measurements[p]	X	X	X	X		X		X	X
Height	X								
Weight and Body Mass Index[q]	X	X						X	X
Waist Circumference		X						X	
Pretreatment Event/ Adverse Events Monitoring[r]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X	X	X		X		X	X
Serum Chemistry[s]	X	X		X				X	X
Hematology	X	X		X				X	X
Urinalysis	X	X		X				X	X
Serum Prolactin[t]	X	X		X				X	X
Hemoglobin A1c (HbA1c)	X	X						X	
Lipid Panel [s]	X	X						X	
Serum Insulin[s]	X	X						X	
High Sensitivity C-Reactive Protein (hs-CRP)	X	X						X	
Hepatitis B/C Panel	X								
Thyroid Panel	X	X						X	
Serum Follicle Stimulating Hormone (postmenopausal women or if menopause is suspected)	X								

Table 2: Schedule of Assessments (Continued)

	Visit 1	Visit 2[a]	Visit 3	Visit 4	TC1[b]	Visit 5	TC2[b]	Visit 6[c]	Visit 7[d]
	Screening Washout[e]	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 EOT/ET	Follow-up
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 35 (± 2)	Day 42 (± 2)	7 (± 2) days after last dose
Serum Pregnancy Test (females of childbearing potential)[u]	X								
Urine Pregnancy Test (females of childbearing potential)[u,v]		X		X				X	X
Urine Drug Screen[v]	X								
Rapid Urine Drug Test[v]		X		X				X	X
Young Mania Rating Scale (YMRS)[w]	X	X	X	X		X		X	X
Physician's Withdrawal Checklist (PWC)[x]								X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[y]	X	X	X	X		X		X	X
Abnormal Involuntary Movement Scale (AIMS)		X						X	
Barnes Akathisia Scale (BARS)		X						X	
Modified Simpson-Angus Scale (SAS)		X						X	
Blood Sampling for Plasma PK and Plasma Prolactin[t,z]	X	X		X				X	X
Optional Blood Sampling for Pharmacogenomic Testing[aa]		X							

Abbreviations: BMI = body mass index; eCRF = electronic case report form; DSM-5 = The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EOT = End of Treatment; ET = Early Termination; hCG = human chorionic gonadotropin; PK = pharmacokinetics; TC = telephone call.

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

[a] Visit 2 is defined as the Baseline Visit. Study drug will be dispensed at Visit 2/Day -1, and subjects will be instructed to take their first dose of study drug the following morning (Day 1).

[b] A telephone call at Day 21 and Day 35 to ascertain adverse events and concomitant medications since last visit.
[c] Visit 6 is the End of Treatment/Early Termination visit. Subjects who discontinue the study prior to Visit 6 will have all Visit 6 procedures performed at the time of discontinuation.
[d] Subjects who discontinue early from the study or complete the study and do not enter the extension study (SEP380-303) will have a safety Follow-up Visit (7 [± 2] days after their last dose of study drug).
[e] Screening assessments may occur over multiple days. Hospitalization during the Screening Period will not be allowed, except where required by local regulations or when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms. Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization. In such cases, a maximum of 7 days' hospitalization during washout of prior medications in the Screening Period will be allowed. An extension of the Screening Period by up to 7 days may be allowed, with prior approval from the Medical Monitor.
[f] Following Informed Consent, the Lifetime Illness Characteristics Questionnaire and the MADRS-S will be completed by the subject prior to other assessments at Screening. Subject must have a MADRS-S total score ≥ 22 at Screening.
[g] For the pre-Baseline review by the Sponsor Eligibility Committee, sites will be required to submit specific Screening information for CRO and Sponsor review, prior to proceeding to Baseline. Details are provided in Section 26, Appendix VII.
[h] Includes a psychiatric history form that will include variables related to duration of illness, treatment response (eg, prior medications used to treat bipolar disorder) and other similar variables.
[i] The SCID-5-CT will be used to support the DSM-5 diagnosis and must be administered by a qualified rater at the site.
[j] Subject eligibility check in IXRS is to be performed prior to randomization, but after all scales are completed, to confirm Blinded Inclusion Criterion 12 is met.
[k] Clinical site staff will record the date and time of the 3 doses prior to the study visit in the source (all visits) and eCRF (Visit 4 [Day 14] and Visit 6 [Day 42] only), based on subject self-report.
[l] Instruct subject to record dosing date and time of the last 3 doses prior to the study visit on the blister pack wallet or other format and bring back all used/unused study drug and packaging to next visit.
[m] Subjects must have a MADRS total score ≥ 22 at Screening (Visit 1) and Baseline (Visit 2). Subjects who demonstrate a decrease (improvement) of ≥ 25% in MADRS total score from Screening (Visit 1) to Baseline (Visit 2) must be screen failed.
[n] The Structured Interview Guide for the HAM-A (SIGH-A) will be used for administration of the HAM-A.
[o] Subjects must have a CGI-BP-S depression score ≥ 4 at Screening (Visit 1) and Baseline (Visit 2).
[p] 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. Respiratory rate and temperature will also be measured.
[q] BMI will be calculated by clinical site staff at Screening (Visit 1) and recorded in the eCRF. At Baseline (Visits 2), Visit 6/EOT/ET (Day 42), and Visit 7 (Follow-up), BMI does not need to be calculated by the clinical site staff as it will be calculated in the analysis.
[r] Events occurring prior to first dose of study drug are programmatically identified as pretreatment events. Events occurring after first dose of study drug are programmatically identified as adverse events.
[s] Subjects are required to fast for at least 8 hours prior to sample collection for laboratory testing at Baseline (Visit 2) and Visit 6/EOT/ET (Day 42). Fasting for 8 hours prior to Screening (Visit 1) is also recommended to avoid potential retests.
[t] Prolactin levels (serum and plasma) will be masked for any assessment collected after the first study drug dose. Prolactin levels prior to the first study drug dose will be unmasked.
[u] For females of childbearing potential, any positive urine ß-hCG test should be confirmed by serum β-hCG.
[v] 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.
[w] To be eligible for enrollment, subjects must have a YMRS total score ≤ 12 at Screening (Visit 1) and Baseline (Visit 2).
[x] The PWC will be completed for early termination subjects and subjects who complete the study and do not rollover into Study SEP380-303; it will not be completed for subjects who rollover into Study SEP380-303.
[y] At the Screening visit (Visit 1), the "Baseline/Screening" version will be completed; for all subsequent visits, the "Since Last Visit" version of the C-SSRS will be administered.

[z] Blood sample for SEP-4199 population pharmacokinetic analysis for R- and S-enantiomers and/or plasma prolactin measurement will be collected at Screening (Visit 1), Baseline (Visit 2), Visit 4 (Day 14), Visit 6/EOT/ET (Day 42), and Visit 7/Follow-up (7 ± 2 days after last dose), with a record of the time of last 3 administered doses on the eCRF at Visit 4 (Day 14) and Visit 6/EOT/ET (Day 42). 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.

[aa] Blood sampling for pharmacogenomic testing will be requested but is not required for participation in the study.

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 events of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BDRM	Blinded data review meeting
BLQ	Below the limit of quantification
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGI-BP-S	Clinical Global Impression – Bipolar Version-Severity of Illness
CI	Confidence interval
COVID-19	Coronavirus disease 2019
Cr	Creatinine
CR	Controlled release
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DBP	Diastolic blood pressure
DBS	Deep brain stimulation
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
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
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
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HLT	High-level term
HR	Heart rate
hs	High sensitivity
ICF	Informed consent form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IR	Immediate release
IRB	Institutional Review Board
ITT	Intention-to-treat
IXRS	Interactive Web Response System
JP	Japan
LDL	Low density lipoprotein
LLN	Lower limit of normal
LOCF	Last observation carried forward

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
MADRS	Montgomery-Asberg Depression Rating Scale
MADRS-S	Montgomery-Asberg Depression Rating Scale, Self-rating Version
MDE	Major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MAOI	Monoamine oxidase inhibitor
mmHg	Millimeters of mercury
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
msec	Millisecond
N	Number of subjects
NMS	Neuroleptic malignant syndrome
PCS	Potentially clinically significant
PD	Pharmacodynamics
PET	Positron emission tomography
PI	Principal Investigator
PK	Pharmacokinetic(s)
POC	Point of care
Pop-PK	Population pharmacokinetics
PP	Per Protocol
PR	Time between P wave and QRS in electrocardiography
PRN	As needed
PT	Preferred term
PVG	Pharmacovigilance
PWC	Physician's Withdrawal Checklist
Q1	First quartile (25^{th} percentile)
Q3	Third quartile (75^{th} 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

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	RR interval
rTMS	Repetitive transcranial magnetic stimulation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SBP	Systolic blood pressure
SCID-5-CT	Structured Clinical Interview for DSM-5-Clinical Trial Version
SD	Standard deviation
SDS	Sheehan Disability Scale
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-A	Structured Interview Guide for the HAM-A
SOC	System organ class
SOP	Standard Operating Procedure
SUSARs	Suspected unexpected serious adverse reactions
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
V	Visit
VCT	Verified Clinical Trials LLC
VNS	Vagus nerve stimulation
WHO-DD	World Health Organization drug dictionary
Wk	Week
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.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during Screening or met study requirements at Screening but was not randomized.
Study Drug (or Study medication)	Term to cover investigational drug and placebo.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and was assigned a randomization number.
Enrolled Subject	Any subject who was successfully screened and enrolled into the Screening period of the study.
Completed Subject	Any subject who participated throughout the duration of the treatment period, up to and including Visit 6.
Early Termination Subject	Any subject who was successfully screened and randomized into the treatment period of the study but did not complete the treatment period of 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

Bipolar spectrum illness (Bipolar I, Bipolar II, Bipolar Disorder NOS) is estimated to affect 4.4% of the population (Merikangas 2007). Bipolar disorder causes more marked functional impairment (Shippee 2011) and has greater impact on quality of life than unipolar depression (Gutierrez-Rojaz 2008). Patients with bipolar depression spend considerably more time in depressive than in manic states over the course of their illnesses (Judd 2002, Judd 2003), and depressive symptoms therefore contribute more to impaired functioning, caregiver/family burden, and economic costs than do manic/mixed symptoms (Miller 2014).

The treatment of bipolar depression is challenging, due to the complexity of clinical presentations, which may include mixed symptoms with depression predominating. Greater depressive illness burden has been associated with increased utilization of complex polypharmacy (Goldberg 2009), and also with greater medical comorbidity in patients with bipolar depression (Magalhaes 2012). Although the pharmacologic treatment of bipolar depression continues to be dominated by three 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). In addition, treatment of bipolar depression with antidepressants remains controversial due to concerns regarding limited efficacy (Ghaemi 2010), and risk of switching patients into mania, hypomania, or rapid cycling (APA 2002).

The clinical efficacy of racemic amisulpride on depressive symptoms in mood disorders (Montgomery 2002) has been demonstrated at dose levels associated with relatively low 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

Sunovion is developing SEP-4199 for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression). The objective of the current study SEP380-301 is to evaluate the efficacy, safety, and tolerability of SEP-4199 controlled release (CR) formulation at doses of 200 mg/day and 400 mg/day compared with placebo in the treatment of subjects with bipolar I depression.

4.3. Risk-Benefit Assessment

The clinical efficacy of amisulpride on depressive symptoms in mood disorders (Montgomery 2002) has been demonstrated at dose levels associated with relatively low D_2 receptor occupancy. 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.

A previous Phase 2 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. Results from this study demonstrated proof-of-concept for SEP-4199 at both fixed doses of 200 mg/day and 400 mg/day in the treatment of bipolar I depression and warrant further development of SEP-4199 at these doses.

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, SEP-4199 CR will be administered in the current study.

5. STUDY OBJECTIVES

The objective of Study SEP380-301 is to evaluate the efficacy, safety, and tolerability of SEP-4199 CR given as monotherapy at fixed doses of 200 mg/day and 400 mg/day compared with placebo in the treatment of subjects with major depressive episode associated with bipolar I disorder (bipolar I depression).

5.1. Primary Efficacy Objective

Evaluate the efficacy of SEP-4199 CR in the reduction of depression symptoms, as measured using the Montgomery-Asberg Depression Rating Scale (MADRS).

5.2. Secondary Efficacy Objective

Evaluate the efficacy of SEP-4199 CR in global improvement of bipolar depression severity, as measured using the Clinical Global Impression-Bipolar Version-Severity of Illness, Depression scale (CGI-BP-S depression).

5.3. Additional Efficacy Objectives

- Assess the proportion of subjects with treatment response, defined as ≥ 50% reduction in MADRS total score.
- Assess the proportion of subjects with depression symptom remission, defined as a MADRS total score ≤ 12.
- Assess the effect of treatment on the core symptoms of depression, as measured using the MADRS-6 subscale, defined as summation of items 1, 2, 3, 7, 8, and 9.
- Assess the effect of treatment in the reduction of anxiety symptoms, as measured using the Hamilton Anxiety Rating Scale (HAM-A).
- Assess the effect of treatment on subject self-rated depression symptom severity, as measured by the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR16).
- Assess the effect of treatment on functional impairment, as measured by the Sheehan Disability Scale (SDS).
- Assess the effect of treatment on quality of life, as measured by the EuroQol-5 Dimension-5 Level (EQ-5D-5L).
- Assess the effect of treatment on anhedonia, as measured by the Snaith-Hamilton Pleasure Scale (SHAPS).

5.4. Safety Objectives

- Determine the incidence of adverse events (AEs), discontinuation due to AEs, serious AEs (SAEs), and adverse events of special interest (AESI).
- Evaluate safety and tolerability using physical examinations, 12-lead electrocardiograms (ECG), vital signs, clinical laboratory tests, prolactin levels, metabolic parameters, body weight, and body mass index (BMI).

- Monitor for akathisia and extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BARS), and Modified Simpson-Angus Scale (SAS).
- Monitor for treatment-emergent mania or hypomania, defined as a Young Mania Rating Scale (YMRS) score of ≥ 16 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania.
- Monitor for suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Evaluate potential withdrawal symptoms using the Physician's Withdrawal Checklist (PWC).

5.5. Pharmacokinetic and Pharmacodynamic Objectives

- Evaluate the therapeutic plasma concentration range of SEP-4199 CR taken as 200 mg/day and 400 mg/day for treatment of major depressive episode associated with bipolar I disorder.
- Perform population pharmacokinetic (Pop-PK) analysis using plasma concentrations of SEP-4199 CR 200 mg/day and 400 mg/day.
- Evaluate the relationship between SEP-4199 PK and plasma prolactin levels for SEP-4199 CR 200 mg/day and 400 mg/day.
- Explore the exposure-response relationship of SEP-4199 CR 200 mg/day and 400 mg/day and symptoms as measured by MADRS using population pharmacokinetic (PK)/ pharmacodynamic (PD) methods.

6. STUDY ENDPOINTS

6.1. Primary Efficacy Endpoint

- Change from Baseline to Week 6 in MADRS total score

6.2. Secondary Efficacy Endpoints

- Change from Baseline to Week 6 in CGI-BP-S depression score

6.3. Additional Efficacy Endpoints

- Change from Baseline in MADRS total score at Weeks 1, 2, and 4
- Change from Baseline in CGI-BP-S depression score at Weeks 1, 2, and 4
- The proportion of subjects with treatment response, defined as ≥ 50% reduction from Baseline in MADRS total score, at Week 6
- The proportion of subjects meeting criteria for remission, defined as MADRS total score ≤ 12, at Week 6
- Change from Baseline to Week 6 in the MADRS-6 core symptoms subscale
- Change from Baseline in HAM-A total score at Weeks 1, 2, 4, and 6
- Change from Baseline to Week 6 in the QIDS-SR16 total score
- Change from Baseline to Week 6 in the SDS total score 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) at Week 6
- Change from Baseline to Week 6 in the EQ-5D-5L Index score and VAS score
- Change from Baseline to Week 6 in the SHAPS total score

6.4. Safety Endpoints

- The incidence of overall AEs, discontinuation due to AEs, and SAEs
- The incidence of hyperprolactinemia-related AESI by sex and overall
- Clinical laboratory evaluations (serum chemistry, hematology, thyroid panel, and urinalysis)
- Clinical evaluations (vital signs including orthostatic effects, and 12-lead ECGs)
- Change and percent change from Baseline to Week 6 in body weight (kg)
- Change from Baseline to Week 6 in BMI (kg/m^2)
- Changes from Baseline in metabolic parameters, including glucose, hemoglobin A1c (HbA1c), insulin, Homeostatic Model Assessment for Insulin (HOMA-IR), total

cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides at Week 6

- Incidence of treatment-emergent mania, defined as a YMRS total score ≥ 16 at two consecutive visits or at final visit, or an AE of hypomania or mania
- Mean changes from Baseline and the proportion of subjects with worsening on the movement disorders scales: AIMS, BARS, and modified SAS at Week 6
- Frequency and severity of suicidal ideation and suicidal behavior as assessed by the C-SSRS
- Occurrence of potential symptoms of withdrawal from SEP-4199 CR measured by change from Week 6 in the PWC total score at the safety Follow-up Visit

6.5. Pharmacokinetic and Pharmacodynamic Endpoints

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

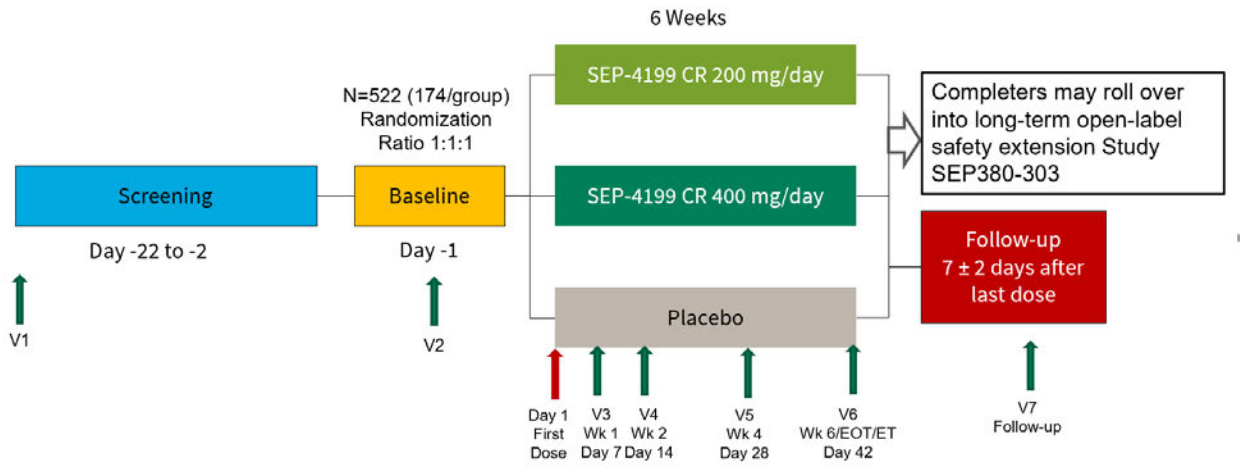
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

SEP380-301 is a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety, and tolerability of treatment with SEP-4199 CR at fixed doses of 200 mg/day or 400 mg/day compared with placebo for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression). The study is projected to randomize approximately 522 subjects in North America, Latin America, Japan, and Europe to SEP-4199 CR 200 mg/day, SEP-4199 CR 400 mg/day, and placebo treatment groups in a 1:1:1 ratio, resulting in approximately 174 subjects/group.

The study will consist of a Screening Period (up to 21 days), a 6-week double-blind Treatment Period (42 days), and a Follow-up Period (7 [± 2] days after the last study drug dose), as shown in the following figure. If necessary, subjects may return to the clinic at any time for an unscheduled visit. Subjects who complete the Treatment Period are eligible to enroll directly into a long-term open-label safety extension study (SEP380-303) of SEP-4199 CR. Those subjects who prematurely discontinue or who complete the Treatment Period and choose not to enroll in the long-term open-label safety extension study will have a follow-up safety Visit 7 (± 2) days after their last dose of double-blind study drug.

Figure 1: Study Schematic



Abbreviations: CR = controlled release; EOT = end of treatment; V = visit; Wk = week
Note: Subjects who do not enroll in long-term open-label safety extension study will have Visit 7.

Screening Period (Visit 1, Day -22 to -2)

Subjects will be evaluated at the Screening Visit (Visit 1) to determine their eligibility to enroll in the study. This visit should be scheduled as an early morning appointment, if possible, due to the recommendation that subjects fast prior to blood sample collection for clinical laboratory tests. Subjects should be advised to obtain and bring medical records as well as any current medications that they are taking. A highly reliable informant (who has had close contact with the

subject and is approved by the Sponsor Eligibility Committee) should be identified to provide collateral information on the subject's psychiatric and treatment history.

Informed consent will be obtained from each subject before any study procedures are performed for this study. Medical, psychiatric, family (eg, biological mother, father, siblings, children) psychiatric and medical, and medication histories will be obtained. Medical history should include information about prior coronavirus disease 2019 (COVID-19) vaccination, infection, and illness, if any. Information supporting a diagnosis of Bipolar I disorder with at least one prior manic episode or manic episode with mixed features must be obtained from additional sources to confirm the Screening evaluation.

The subject's eligibility assessments will be reviewed by the Sponsor Eligibility Committee, which consists of the contract research organization's (CRO) medical team along with the Sponsor and sponsor designees based on protocol-specified inclusion and exclusion criteria (see Section 26, Appendix VII for details). The Sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility. In the event the Sponsor Eligibility Committee and Investigator do not agree on a subject's eligibility, then the subject will not be approved to proceed to the Baseline Visit (Visit 2).

Subjects will discontinue and wash out prior or concomitant medications, as applicable, prior to Baseline. Psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) are to be discontinued as tolerated and clinically appropriate at least 3 days or 5 half-lives (whichever is longer) prior to Baseline.

Hospitalization during the Screening Period will not be allowed, except

- where required by local regulations, or
- when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms.

Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization. In such cases, a maximum of 7 days' hospitalization during washout of prior medications in the Screening Period and a maximum of 7 days' hospitalization during Week 1 of study medication dosing will be allowed. If an extension is required, medical justification must be provided to the Medical Monitor and the Medical Monitor, following Sponsor review, must approve the request to extend the duration of hospitalization.

To determine subject eligibility, abnormal Screening clinical laboratory tests may only be repeated after discussion with the Medical Monitor.

To determine subject eligibility, the Screening ECG may be repeated in the event of technical difficulty or error associated with the first ECG or if clinically indicated. Subjects should rest supine for at least 10 minutes prior to all ECGs.

All Screening assessments should be completed in sufficient time for Site and CRO/Sponsor to receive and review results prior to the Baseline Visit (Visit 2). If necessary, to ensure receipt and review of all Screening information, an extension of the Screening Period by up to 7 days may be allowed, with prior approval from the Medical Monitor.

Subjects who meet all inclusion criteria and no exclusion criteria after full evaluation of Screening data may proceed to the Baseline Visit (Visit 2) after receiving approval from the Sponsor Eligibility Committee.

Baseline Visit (Visit 2, Day -1)

Subjects who meet eligibility criteria during the Screening Period will return to the study site on Day -1 for confirmation of Screening evaluations as well as completion of pre-dose assessments. Subjects who continue to meet all inclusion criteria and no exclusion criteria at Baseline will be randomized and dispensed study drug at Day -1.

Double-blind Treatment Period (Visits 3-6, Days 1 to 42)

Subjects will self-administer the study drug on an outpatient basis once daily with or without food beginning on the morning of Day 1 (the day after the Baseline Visit [Visit 2]) and continue for 6 weeks. Subjects will be instructed to administer study drug as a single oral dose at approximately the same time each morning. Subsequent clinic visits should be scheduled to begin no later than 6 hours post-dose, if possible. The last dose of study drug will be self-administered by the subject at home on the morning of Visit 6 (Day 42).

During the Treatment Period, subjects will have clinic visits as follows: Visit 3 (Day 7), Visit 4 (Day 14), and Visit 5 (Day 28). Telephone calls to ascertain AEs and concomitant medications will be scheduled on Days 21 and 35. In order to facilitate scheduling of clinic visits and telephone calls, a window of ± 2 days will be allowed for each clinic visit and telephone call.

End of Treatment (EOT)/Early Termination (ET) (Visit 6, Day 42 [± 2 days])

Subjects will have a clinic visit at Visit 6 (Day 42) for efficacy and safety assessments. Subjects who complete the 6-week double-blind Treatment Period will be considered study completers, and may be eligible to enroll directly into a long-term open-label safety extension study of SEP-4199 CR (SEP380-303).

Subjects who prematurely discontinue the study will undergo an Early Termination (ET) visit at the time of discontinuation. The ET Visit will include all efficacy and safety assessments scheduled for Visit 6 (Day 42). Prematurely discontinued subjects will not be eligible for the long-term open-label safety extension study.

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

All subjects who received at least one dose of study drug and who do not enroll in the subsequent open-label safety extension study will have a Follow-up Visit for safety and tolerability assessments 7 (± 2) days after their last dose of double-blind study drug. Assessment of potential withdrawal effects will also be made during the Follow-up Period. During the Follow-up Period, completed subjects who do not continue into an open-label safety extension study will not be allowed to initiate treatment with a psychotropic medication until after completion of the Follow-up Visit. In the event that the severity of major depressive episode (MDE) symptoms at the Week 6 EOT/ET visit is judged to present a safety risk to complying with this requirement, the subject should be discontinued from the study and managed as clinically appropriate by the Investigator.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

Subjects who successfully meet eligibility criteria will be randomly assigned to receive SEP-4199 CR 200 mg/day, SEP-4199 CR 400 mg/day, or matching placebo in a double-blind fashion in a 1:1:1 ratio. The randomization will be balanced using permuted blocks with stratification factor of countries. The stratification process will be handled in an Interactive Web Response Systems (IXRS).

At the Baseline Visit (Visit 2), the treatment code, which is linked to the randomization schedule, will be assigned by the IXRS designated by the Sponsor. A unique subject number will be assigned by the IXRS when a subject enters the Screening Period. Each subject will be given one subject number comprised of 9 digits. Each subject number will specify the study (3 digits), site (3 digits), and subject (3 digits) (eg, 301001001 would denote: Study 301, Site 001, and Subject 001). If a subject does not meet study entry criteria, his or her subject number cannot be reassigned to another subject.

Subjects may be screened up to a maximum of 3 times, if judged appropriate by the Investigator and approved by the Medical Monitor. Each time the subject is rescreened, they will be reconsented and receive a new subject number, which cannot be reassigned to another subject. Subjects who do not pass Inclusion Criterion#12 (ie, subject meets an additional inclusion criterion at Baseline that will remain blinded to clinical site Investigators and staff) may not be re-screened.

7.2.2. Blinding

Subjects, Investigators, clinical site staff, persons performing the assessments, clinical operations personnel (including the Sponsor's bioanalytical manager), data analysts, personnel at central laboratories (including imaging), and the Sponsor will remain blinded to randomization scheme until blinding is formally broken for all subjects. For this to occur, all subjects must have completed the study and the study database must be locked.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: bioanalytical laboratory personnel involved in the analysis of PK samples, Data and Safety Monitoring Board (DSMB) members involved in regular review of safety data, external statistical staff involved in preparing materials for DSMB reviews, and the Sponsor's clinical trials materials management.

Prolactin levels will be masked in regular lab data transfer for any assessment collected after the first study drug dose and until database is locked and treatment is unblinded (that is to say, prolactin assessed prior to the first study drug dose will be unmasked and available for study personnel during the study).

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, and appearance.

Plasma concentrations of aramisulpride, esamisulpride, and total amisulpride will not be disclosed before unblinding. In any case that concentration data transfer to the Sponsor becomes necessary prior to the database lock, then the concentration data can only be shared with the Sponsor's bioanalytical project manager with dummy subject IDs.

7.2.3. Emergency Unblinding Procedures

In the case of a medical emergency, where knowledge of study drug by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IXRS. The date and reason for unblinding are to be documented in the source documents. Any subject for whom the treatment assignment was unblinded is to be discontinued from further study participation. The subject should return for a final study assessment as described in Section 11.8.4. The identity and responsibility of those individuals at the study site who gain access to the unblinded treatment assignment must be documented. It is mandatory that all personnel who are involved in the unblinding, and who have access to the unblinded treatment assignment, maintain the confidentiality of the information and do not divulge the treatment assignment.

7.3. Rationale

7.3.1. Rationale for the Study Design

Sunovion is developing SEP-4199 for the treatment of major depressive episode associated with bipolar I disorder (bipolar I depression). The objective of the current study SEP380-301 is to evaluate the efficacy, safety, and tolerability of SEP-4199 CR at doses of 200 mg/day and 400 mg/day compared with placebo in the treatment of subjects with bipolar I depression.

A previous Phase 2 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. Results from this study demonstrated proof-of-concept for SEP-4199 IR at both fixed doses of 200 mg/day and 400 mg/day in the treatment of bipolar I depression and warrant further development of the SEP-4199 compound at these doses.

A novel CR formulation of SEP-4199 has been developed. SEP-4199 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, SEP-4199 CR will be administered in the current study.

7.3.2. Rationale for the Dosages

The hypothesized therapeutic dose range of SEP-4199 is 200 mg/day to 400 mg/day based on results from pharmacology studies in human volunteers and a completed Phase 2 clinical study of SEP-4199 IR (Study SEP380-201) in 337 subjects with bipolar I depression. This dose range will be confirmed in the current fixed-dose study of SEP-4199 CR.

Fixed doses of 200 mg/day and 400 mg/day were previously selected for clinical evaluation based on a demonstrated pharmacodynamic effect of $5HT_7$ receptor antagonism, and moderate dopamine D_2 receptor occupancy within this dose range. The unique pharmacology of SEP-4199 at doses of 200 mg/day to 400 mg/day is hypothesized to be optimal for the treatment of bipolar I depression while minimizing the extrapyramidal symptoms associated with high levels of D_2 receptor antagonism.

In a previously completed Phase 2 study (SEP380-201) in 337 subjects from the US, Europe, and Japan with bipolar I depression, SEP-4199 administered as the IR formulation at fixed doses of 200 mg/day and 400 mg/day demonstrated proof of concept in the treatment of bipolar I depression. On the prespecified primary analysis of change from Baseline to Week 6 on MADRS total score in a cohort of US and European subjects (N = 289), SEP-4199 IR 200 mg/day and 400 mg/day doses resulted in similar numerical improvements compared to placebo but just missed significance (adjusted p = 0.054 for both treatment groups) due to higher-than-anticipated placebo response and variability. For the full global intention-to-treat (ITT) population including US, European, and Japanese subjects (N = 337), both doses of SEP-4199 demonstrated significantly greater change from Baseline to Week 6 in MADRS total score compared to placebo (post-hoc adjusted p = 0.025 for both treatment groups using the same multiplicity adjustment approach). Results based on the full global ITT population strengthened the evidence in favor of efficacy at both SEP-4199 IR doses.

Efficacy results for the 200 mg/day and 400 mg/day doses were generally highly similar on all primary, key secondary, and additional secondary endpoints. However, in the primary analysis cohort of US and European subjects, the odds vs. placebo of achieving remission (defined as MADRS ≤ 12 at Week 6), while not significant for the 200 mg/day group, were significantly greater for the 400 mg/day group (p = 0.024). This result suggests that some subjects may have derived greater benefit from the higher dose and warrants further evaluation of both 200 mg/day and 400 mg/day doses.

SEP-4199 IR at fixed doses of 200 mg/day and 400 mg/day was well tolerated in the Phase 2 SEP380-201 study. For the full global safety population, rates of discontinuation due to an AE were similar in the 200 mg/day (8.8%) and 400 mg/day (7.0%) SEP-4199 IR treatment groups, and higher than in the placebo group (1.8%). The only AE with incidence reflecting a dose-response relationship was ECG QTc prolonged, which was reported for 9 subjects in the 400 mg/day treatment group and 0 subjects in the 200 mg/day and placebo groups; however, none of the subjects in the 400 mg/day group also reported an AE in the Cardiac Disorders Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC). As Study SEP380-105 demonstrated that the lower C_{max} of the CR formulation was associated with substantially lower QTc prolongation than the IR formulation, an improved therapeutic index with regard to cardiac safety is expected in the current study.

The incidence of mania or hypomania was higher in the SEP-4199 IR 200 mg/day group (4.4%) than in the 400 mg/day group (0.9%). This finding suggests the possibility that the 400 mg/day dose may provide additional benefit in mood stabilization by virtue of its greater D_2 receptor antagonism.

Most other AEs occurred at comparable rates in the two SEP-4199 IR groups. Marked prolactin elevation (≥ 5x upper limit of normal [ULN]) was observed in 79% of female subjects who received SEP-4199 IR in this study. A total of 10 (4.4%) subjects reported hyperprolactinemia-related AEs, of which the most common was galactorrhea, reported in 3 (2.7%) subjects in the 200 mg/day group and 4 (3.5%) subjects in the 400 mg/day group. Racemic amisulpride is known to increase prolactin levels; therefore, the prolactin elevation observed with SEP-4199 IR treatment in the completed study was expected. The data demonstrate that a relatively small proportion of subjects with increased prolactin levels is likely to experience any AEs.

Taken together, these results demonstrated proof of concept for the efficacy of SEP-4199 IR at doses of 200 mg/day and 400 mg/day for the treatment of bipolar I depression. They further show that SEP-4199 IR treatment was well tolerated at these doses; and SEP-4199 CR is hypothesized to be therapeutically equivalent to SEP-4199 IR based on the SEP380-105 study but with an improved therapeutic index due to improved cardiac safety, suggesting a positive benefit/risk that supports further clinical development of SEP-4199 CR in this dose range for the treatment for bipolar I depression.

7.3.3. Rationale for the Study Population

The subject population includes males and females ranging from 18 to 65 years of age, and in concert with standard practice guidelines, will be required to have a diagnosis of bipolar I disorder, whose most recent episode is depressed with or without rapid cycling disease course (≥ 4 episodes of mood disturbance but < 8 episodes in the previous 12 months) with or without psychotic features (diagnosed by DSM-5 criteria, and confirmed by the SCID-5-CT). The current episode of major depression associated with bipolar I disorder will be confirmed by the Investigator and noted in the source records.

7.3.4. Rationale for the Endpoints

The efficacy assessments and their timing are considered appropriate to assess the efficacy 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 on these parameters. The standard safety assessments and their timing are appropriate to assess the safety of SEP-4199 in adults with bipolar I depression.

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 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.

Refer to Section 15.4.7 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

Attempts should be made to obtain relevant medical and pharmacy records for subjects during screening. This is strongly encouraged to confirm past diagnoses and treatment history.

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 or legally acceptable representative must possess an educational level and degree of understanding of English or the local language that enables them to communicate suitably with the Investigator and the study coordinator.
3. Subject is 18 to 65 years of age, inclusive, at the time of informed consent.
4. Subject meets DSM-5 criteria, based on the SCID-5-CT, for bipolar I disorder, current episode depressed with or without rapid cycling disease course (≥ 4 episodes of mood disturbance but < 8 episodes in the previous 12 months) with or without psychotic features.
5. Subject has a lifetime history of at least 1 manic episode or manic episode with mixed features corroborated by at least one of the following: medical records, documented correspondence with a treating psychiatrist or mental healthcare provider/staff, or information from a reliable informant who is familiar with the subject's psychiatric history. The adequacy of the information will be assessed by the Sponsor Eligibility Committee.
6. Attempts should be made to obtain supporting information regarding the subject's current major depressive episode from additional sources. This may include relevant medical records, or documented correspondence with a treating psychiatrist or mental healthcare provider/staff if the subject has been evaluated during the current MDD episode, or information from a reliable informant who is familiar with the subject's recent psychiatric history.
7. Subject's current major depressive episode is ≥ 4 weeks and less than 12 months in duration at Screening.
8. Subject has a MADRS-S total score ≥ 22 at Screening.
9. Subject has a MADRS total score ≥ 22 at both Screening and Baseline.
10. Subject has a CGI-BP-S depression score ≥ 4 at both Screening and Baseline.
11. Subject has a YMRS total score ≤ 12 at both Screening and Baseline.
12. Subject meets an additional inclusion criterion at Baseline that will remain blinded to clinical site Investigators and staff.
13. 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.

14. Female subjects of childbearing potential must have a negative serum ß-hCG test at Screening and a negative urine pregnancy test at Baseline.
15. Male subjects agree to avoid fathering a child and to use effective methods of birth control throughout the study and for at least 90 days after the last study drug administration. Contraception requirements are detailed in Section 10.4.
16. Subject is in good physical health, based on medical history, physical examination, neurological examination, vital signs, ECGs, and results of clinical laboratory tests (hematology, chemistry, and urinalysis).
17. Subjects with type 2 diabetes are eligible for study inclusion only if all following conditions are met:
    - Subject's random (non-fasting) blood glucose is < 200 mg/dL (11.1 mmol/L) or fasting blood glucose < 126 mg/dL (7.0 mmol/L) at Screening.
    - Subject's HbA1c is ≤ 7.0% at Screening.
    - If a subject is currently being treated with oral hypoglycemics, the dose has been stable for at least 30 days prior to Screening. (Such medication may subsequently be adjusted or discontinued during the study, as clinically indicated.)
    - Subject has not required hospitalization for diabetes or related complications in the 12 months prior to Screening.
    - Subject's type 2 diabetes was not newly diagnosed at Screening.
18. Subject who requires concomitant medication treatment with the following agents may be included if they have been on stable doses for the specified times below, and if the subject's medical condition is deemed clinically stable following consultation with the Medical Monitor.
    - Oral hypoglycemics must be stable for at least 30 days prior to Screening.
    - Thyroid hormone replacement must be stable for at least 90 days prior to Screening.
    - Anti-hypertensive agents must be stable for at least 30 days prior to Screening.
19. Subject is approved by the Sponsor Eligibility Committee to proceed to the Baseline Visit following review of all required information collected at Screening. See Section 26, Appendix VII for details.

8.2. Subject Exclusion Criteria

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

1. Subject currently has any DSM-5 defined psychiatric diagnosis other than bipolar I disorder that was the primary focus of treatment or that is currently being treated with concomitant medication.

2. Subject has a lifetime history of or symptoms consistent with schizophrenia, schizoaffective disorder, or a major psychiatric diagnosis other than bipolar I disorder that is judged to pose risk to the study scientific objectives based on the judgement of the Investigator or the Sponsor Eligibility Committee. A lifetime history of anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD) are not exclusionary if the disorder does not meet Exclusion Criterion #1.(**Note:** Subjects with a previous diagnosis of major depressive disorder or bipolar II disorder that was subsequently changed to bipolar I disorder are allowed.)
3. Subject has a history within the past 12 months prior to Screening of substance use disorder.
4. Subject has confirmed or suspected borderline personality disorder.
5. Subject demonstrates a decrease (improvement) of ≥ 25% in MADRS total score from Screening to Baseline.
6. Subject is considered by the Investigator to be at imminent risk of suicide or injury to self or others, or has a score ≥ 4 on MADRS item 10 (suicidal ideation), 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 the Screening Visit (in the past 3 months [90 days]) or at Baseline.
7. Subject has received any psychotropic medication or herbal supplement within 3 days or 5 half-lives (whichever is longer) prior to Baseline or anticipates the need for psychotropic medications or herbal supplements during participation in this study, with the exception of the medications specified in Section 10.3. The following treatments have additional restrictions as specified below:
    a. Monoamine oxidase inhibitors (MAOIs) must be discontinued at least 28 days prior to Baseline.
    b. Fluoxetine, and olanzapine/fluoxetine combination must be discontinued at least 28 days prior to Baseline.
    c. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to Baseline. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation.
    d. Depot neuroleptics must have been discontinued at least one treatment cycle or at least 30 days (whichever is longer) prior to Baseline.
    e. Subjects with a history of treatment with ketamine, esketamine, arketamine, or psychedelic therapies (eg, psilocybin, methylenedioxymethamphetamine [MDMA]) for major depressive disorder (MDD) or any psychedelic treatment.
    f. Electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) within 90 days prior to Baseline.
    g. Subjects with a history of treatment with vagus nerve stimulation (VNS) or deep brain stimulation (DBS) are excluded from study participation.

8. Subject initiated a new psychotherapeutic intervention (eg, psychotherapy) focused on treatment of bipolar I depression within the past 12 weeks prior to Screening. (**Note:** Subjects who have participated in ongoing psychotherapy treatment for at least 12 weeks prior to Screening will be permitted to continue this treatment during the study.)
9. Subject has a history of non-response to an adequate (6-week) trial of 3 or more antidepressants (with or without mood stabilizers) during the current major depressive episode.
10. Subject was hospitalized during the Screening Period without explicit approval by Medical Monitor. (**Note:** Hospitalization during the Screening Period will not be allowed, except where required by local regulation or when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms. Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization.)
11. Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that would pose a risk to the subject or that might confound the results of the study. (**Note:** Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to subject or study results. In cases in which the impact of the condition upon risk to subject or study results is unclear, the Medical Monitor should be consulted.)
    a. Hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular (including unstable hypertension), hepatic, neurologic, or allergic disease that is clinically significant or unstable (except for seasonal allergies at time of dosing). (**Note**: Any subject with a known cardiovascular disease or condition, including hypertension, [even if under control and considered stable] must be discussed with the Medical Monitor before being randomized in the study.)
    b. Chronic organic disease of the CNS such as tumors, inflammation, active (or history of) seizure disorder, vascular disorder, Parkinson's disease, Alzheimer's disease or other forms of dementia, myasthenia gravis, or other degenerative processes. Subject has history of intellectual disability or persistent neurological symptoms attributable to serious head injury. (**Note**: Past history of febrile seizure is not exclusionary.)
    c. Evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation. Subjects who test positive for hepatitis C antibody at Screening and have a positive or indeterminate confirmatory test for hepatitis C are excluded. Subjects who test positive for hepatitis B surface antigen at Screening are excluded.
    d. History of any cardiovascular disorder/condition known to increase the possibility of QT prolongation, history of additional risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome or Brugada Syndrome) or cardiac conduction disorders, or requires treatment with an antiarrhythmic medication.
    e. History of neuroleptic malignant syndrome (NMS).
    f. History of malignancy < 5 years prior to the Screening Visit, except for adequately treated basal cell carcinoma or squamous cell skin cancer or in situ cervical cancer.

Subjects with lifetime history of pituitary tumors, including pituitary adenomas, of any duration are excluded.

g. History of a condition (including history of malabsorption) or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, bowel resection) that could interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH.
h. Known history of human immunodeficiency virus (HIV) seropositivity.
i. Type 1 diabetes or insulin-dependent type 2 diabetes.

12. Subject with a supine systolic blood pressure (SBP) ≥ 150 mmHg and/or supine diastolic blood pressure (DBP) ≥ 95 at Screening or Baseline. A repeat blood pressure measurement is allowed once during the Screening Period and once at Baseline. The repeat measurements can be used to determine eligibility. The repeat blood pressure measurement at Screening can be conducted on a different day within the Screening Period, if needed.
13. Subject has a body BMI ≥ 40 or < 18 kg/m^2 at Screening.
14. Subject has a clinically significant abnormal 12-lead ECG at Screening (based on central cardiologist review) or Baseline (based on machine reading), including:

- QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 milliseconds (msec) (males) or > 470 msec (females)
- QRS > 110 msec
- PR > 220 msec
- Second- or third-degree atrioventricular block
- Any rhythm other than sinus rhythm, that is interpreted by the Investigator to be clinically significant
- Heart rate (HR) < 50 beats per minute (bpm)
- HR > 100 bpm

15. Subject requires treatment with a drug that is associated with an increase in QTc interval (see Section 24, Appendix V for a list of medications, not all inclusive).
16. Subject has a first degree family history of QTc prolongation or unexplainable sudden death at < 50 years of age.
17. Subject has any laboratory test result at Screening that indicates a clinically significant medical condition. These include but are not limited to the following test results. Clinical significance of other abnormalities will be based on Investigator judgment in consultation with the Medical Monitor.

- Thyroid stimulating hormone (TSH) ≤ 0.5x lower limit of normal (LLN) or ≥ 1.25x ULN (regardless of whether T3 and T4 are within the normal reference range)
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3x ULN
- Creatinine clearance ≤ 60 ml/min

- Serum blood urea nitrogen (BUN) or serum creatinine (Cr) value ≥ 1.5x ULN
- Fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L). (**Note:** Subjects with fasting blood glucose from 100-125 mg/dL [5.6-6.9 mmol/L] may enter the study based on the approval of the Medical Monitor. Subjects who are found to have been non-fasting at Screening may be allowed if their random [non-fasting] blood glucose is < 200 mg/dL [11.1 mmol/L]. Subjects with random [non-fasting] blood glucose at Screening ≥ 200 mg/dL [11.1 mmol/L] must be retested in a fasted state.)
- HbA1c > 7.0%

18. Subject has a prolactin concentration > 100 ng/mL at Screening.
19. Subject exhibits evidence of severe tardive dyskinesia, severe dystonia, or any other severe movement disorder, as judged by the Investigator.
20. Subject tests positive for drugs of abuse at Screening. In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the Investigator will evaluate the subject's ability to abstain from cannabis during the study. This information will be discussed with the Medical Monitor for study enrollment consideration. However, a positive test urine drug screen may not result in exclusion of subjects if the Investigator determines that the positive test is a result of prescription medicine(s), and the medication can be safely washed out prior to Baseline and confirmed by a repeat urine drug screen.
21. Subject tests positive for any drug of abuse or cannabis on rapid urine drug test at Baseline.
22. Subject has a history of allergic reaction or suspected sensitivity to amisulpride, any other substance that is contained in the study drug formulation, or to more than two distinct chemical classes of drug (eg, sulfas and penicillins).
23. Subject who is lactating or plans to get pregnant during the study.
24. Subject has received any investigational drug product within 90 days prior to signing informed consent or has participated in more than 3 studies in psychiatric indications of investigational drug products within their lifetime.
25. Subject previously randomized in a SEP-4199 clinical study.
26. Subject is in the opinion of the Investigator, Medical Monitor and/or Sponsor, unsuitable in any other way to participate in this study.

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 group, each dose of study drug will consist of 1 x 200 mg tablet and 1 x matching placebo tablet.
- For the SEP-4199 CR 400 mg/day group, each dose of study drug will consist of 2 x 200 mg tablets.
- For the placebo group, each dose of study drug will consist of 2 x matching placebo 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	Matching Placebo
Dosage form	Tablets	Tablets
Unit dose	Tablet	Tablet
Route of administration	Oral	Oral
Physical description	Pale orange round film-coated unmarked tablets	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 Placebo also contains microcrystalline cellulose. Placebo does not contain partially hydrolyzed pregelatinized starch and partially hydrolyzed polyvinyl alcohol.	

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 18 tablets of SEP-4199 CR 200 mg or Placebo tablets. Each blister card will be arranged in nine columns and two rows. 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 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 one to two 9-day (7 days + 2 extra days) blister cards per scheduled visit, depending on the timing of the next scheduled visit (see Table 2). IXRS drug dispensing guidelines should be followed for dispensing study drug to subjects. A specific user manual will be provided.

The first study drug dose will be taken on Day 1. Subjects will take a column of two tablets 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/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 and placebo 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 6 (Day 42).

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

Prior psychotropic and non-psychotropic medications taken during the 60 days prior to Screening will be recorded on the electronic case report form (eCRF) at the Screening Visit (Visit 1).

If the duration of the current major depressive episode is > 60 days, then all psychotropic medications taken since the onset of the current major depressive episode will be recorded on the eCRF.

Every effort should be made to collect medical and/or pharmacy records for psychotropic and non-psychotropic medications recorded on the eCRF. However, if medical records cannot be obtained, prior medications are to be reported based on subject and highly reliable informant report.

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 eCRF. Medication name, dose, frequency, route, start date, stop date, and indication 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).

Initiation of new psychotherapeutic interventions (eg, a new course of psychotherapy) will not be permitted during the study. Subjects who have participated in ongoing psychotherapy treatment

for at least 12 weeks prior to Screening will be permitted to continue this treatment during the study.

During the Follow-up Period, completed subjects who do not continue into an open-label safety extension study will not be allowed to initiate treatment with a psychotropic medication until after completion of the Follow-up Visit.

10.3.1. Prior Medications

Treatment with all prior psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) and herbal supplements must be discontinued as tolerated and clinically appropriate at least 3 days or 5 half-lives (whichever is longer) prior to Baseline. Subjects treated with MAOIs, fluoxetine, or olanzapine/fluoxetine combination must discontinue these medications at least 28 days prior to Baseline. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to Baseline. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation. Depot neuroleptics must be discontinued at least 30 days or one treatment cycle (whichever is longer) prior to Baseline. Subjects who, in the opinion of the Investigator, cannot safely discontinue prior psychotropic medications, are not eligible for the study and will be screen failed.

10.3.2. Concomitant Non-psychotropic Medications

Medications for short-term (no more than 10 days) treatment of a medical condition are allowed provided that the medications do not prolong the QTc interval. Section 24, Appendix V provides a representative, but not exhaustive, list of medications that prolong the QT interval and are not allowed during the study. Non-psychotropic medications used to treat mild, chronic medical conditions may be used during Screening and after Baseline if the dose and regimen have been stable (± 25%) for at least 30 days prior to Screening. The concomitant medication dose may change as needed after Screening. β-adrenergic antagonists used to treat stable hypertension may be continued. In addition, use of non-prescription pain medications (eg, aspirin, acetaminophen/paracetamol, ibuprofen) is 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 used to treat movement disorders should be tapered and discontinued 3 days or 5 half-lives (whichever is longer) prior to Baseline but may be reinstituted 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 during Screening and for Weeks 1-3 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.

10.3.4. Prohibited Medications

Treatment with all prior psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) must be discontinued as tolerated and clinically appropriate at least 3 days or 5 half-lives (whichever is longer) prior to Baseline. Subjects treated with MAOIs, fluoxetine, or olanzapine/fluoxetine combination must discontinue these medications at least 28 days prior to Baseline. Clozapine used at 200 mg/day or less for insomnia, agitation, or anxiety must be discontinued at least 28 days prior to Baseline. Subjects with a history of treatment with clozapine for any reason at doses greater than 200 mg/day or at doses less than or equal to 200 mg/day for a usage other than insomnia, agitation, or anxiety are excluded from study participation. Depot neuroleptics must have been discontinued at least 30 days or one treatment cycle (whichever is longer) prior to Baseline.

Treatment with sedative hypnotics (for insomnia) is permitted during the Screening Period, but should be tapered as clinically appropriate to ensure the subject meets and can comply with the protocol-specified dosing limitations applicable to these agents following Baseline (see Section 10.3.3).

Medications that prolong the QTc interval are prohibited during the study. For a list of these medications, please see Section 24, Appendix V.

The use of herbal supplements for any reason is prohibited during trial participation and must be discontinued at least 3 days or 5 half-lives (whichever is longer) prior to Baseline. The use of dietary supplements (eg, omega fatty acids) or other complementary or alternative medications for treating depression during the trial is not permitted.

With the exception of benztropine, biperiden, trihexyphenidyl, diphenhydramine, propranolol, and amantadine (or their equivalent as agreed by the Medical Monitor) as specified in Section 10.3.3, medications used to treat movement disorders (including levodopa) are prohibited.

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 as determined by the central laboratory

-OR-

- Childbearing potential with a negative serum pregnancy test at Screening 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.
    - Vasectomised 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 for 30 days after last dose of the study drug.

10.5. Guidance for Overdose

The effects of an overdose of SEP-4199 CR 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) and will be asked to give explicit consent by signing this separate patient information and consent form. Where allowed under local laws and regulations, such consent from subjects is a precondition for being able to participate in this clinical study. 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, medical history, psychiatric history, and prior and concomitant medication use will be collected.

Demographics collected at Screening will include sex, race, ethnicity, date of birth, weight, and height, as allowed per region.

Clinical site staff will calculate and record BMI at Screening. BMI for all other visits will be calculated in the analyses.

Waist circumference will be measured in inches or centimeters and recorded in the eCRF.

For medical history, only relevant/significant medical history and recurrence of any condition will be collected.

11.3. Diagnostic and Symptom Severity Scales to Inform Subject Eligibility

11.3.1. Lifetime Illness Characteristics Questionnaire

The Lifetime Illness Characteristics Questionnaire will be administered at Screening, prior to other Screening assessments. The Lifetime Illness Characteristics Questionnaire is a subject-reported computerized assessment that establishes disease-related life history across 5 dimensions: hypomania or mania, age of onset of first mood symptoms, illness course and other features generally only visible over time, response to medications (antidepressants and mood stabilizers), and family history of mood and substance use disorders. Subject responses are used to calculate a Bipolarity Index Score. A score ≥ 50 is associated with a high likelihood of a diagnosis of bipolar disorder (Aitken 2015).

11.3.2. SCID-5-CT

The Structured Clinical Interview for DSM-5 (SCID-5) is the most widely used structured diagnostic instrument for assessing DSM-5 disorders. The SCID-5 is organized into diagnostic modules, and it assesses mood disorders, psychotic disorders, substance use disorders, anxiety disorders, obsessive–compulsive and related disorders, eating disorders, somatic symptom disorders, some sleep disorders (ie, insomnia and hypersomnolence disorders), "externalizing disorders" (ie, intermittent explosive disorder, gambling disorder, and adult attention deficit hyperactivity disorder), and trauma- and stressor-related disorders. The SCID-5 for clinical trials (SCID-5-CT; First 2015) will be utilized to confirm the diagnosis of bipolar I depression for this study.

The SCID-5-CT will be administered by a qualified rater at the site. The SCID-5-CT 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 SCID-5-CT to determine study eligibility will be provided in the Study Reference Manual.

11.3.3. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS will be administered at Screening and Baseline to determine subject eligibility. Subjects will be required to have moderate-to-severe depression symptoms, as demonstrated by a MADRS total score ≥ 22 at both Screening and Baseline. In addition, subjects having a decrease (improvement) of ≥ 25% in MADRS total score from Screening to Baseline will be excluded from study participation.

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.

11.3.4. Montgomery-Asberg Depression Rating Scale, Self-rating Version (MADRS-S)

The MADRS-S is a computerized version of the MADRS assessment (Fantino 2009) that the subject will complete at the Screening Visit prior to the clinician-administered MADRS interview. The self-rating version of the MADRS has been validated against the clinician-administered MADRS (Mundt 2006). A MADRS-S score ≥ 22 will be required at Screening for subject eligibility. The MADRS-S will additionally be used to ascertain the reliability of site clinician-administered MADRS assessment at Screening.

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

The CGI-BP-S will be administered at Screening and Baseline to determine subject eligibility. A CGI-BP-S depression score ≥ 4 (moderate) will be required at Screening and Baseline.

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 CGI-BP-S scores will be provided in the Study Reference Manual.

11.3.6. Young Mania Rating Scale (YMRS)

The YMRS will be administered at Screening and Baseline to determine subject eligibility. Subjects must have a YMRS total score ≤ 12 at both the Screening and Baseline Visits.

The YMRS is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar disorder. The 11 items are: Elevated Mood, Increased Motor Activity Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language-Thought Disorder, Content, Disruptive-Aggressive Behaviour, Appearance, and Insight. The YMRS is a clinician-rated assessment.

The YMRS will be administered by a qualified rater at the site. Further information regarding administration of the YMRS, including rater training and certification as well as recording of YMRS scores to determine study eligibility, will be provided in the Study Reference Manual.

11.4. Efficacy Assessments

11.4.1. Montgomery-Asberg Depression Rating Scale (MADRS)

In addition to administration of the MADRS at Screening and Baseline to determine subject eligibility, the MADRS will be administered at post-Baseline study visits during the Treatment Period (Visits 3, 4, 5, and 6 at Days 7, 14, 28, and 42, respectively) as an efficacy assessment. See Section 11.3.3 for a description of the MADRS instrument.

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

In addition to Screening and Baseline, the CGI-BP-S will be administered at post-Baseline study visits during the Treatment Period (Visits 3, 4, 5, and 6 at Days 7, 14, 28, and 42, respectively) as an efficacy assessment. See Section 11.3.5 for a description of the CGI-BP-S instrument.

11.4.3. Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a clinician-administered scale that will be administered at Baseline, and at post-Baseline study visits during the Treatment Period (Visits 3, 4, 5, and 6 at Days 7, 14, 28, and 42, respectively).

The HAM-A is a rating scale 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.

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

The QIDS-SR16 is a 16-item subject-reported depression symptom severity questionnaire that will be completed at Baseline and Visit 6 (Day 42).

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.

11.4.5. Sheehan Disability Scale (SDS)

The SDS is a subject-reported assessment of function that will be completed at Baseline and Visit 6 (Day 42).

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.

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

The EQ-5D-5L is a quality of life assessment that the subject will complete at Baseline and Visit 6 (Day 42).

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of 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 5 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.

11.4.7. Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS (Snaith 1995) is a subject-reported questionnaire that will be administered at Baseline and Visit 6 (Day 42).

The SHAPS is a 14-item scale that assesses 4 domains of hedonic experience: interests/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.

11.5. Safety Assessments

11.5.1. Adverse Events

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

AEs and SAEs will be monitored throughout the study at all visits.

11.5.2. Clinical Laboratory Tests

Subjects are required to fast for at least 8 hours prior to sample collection for laboratory testing at Baseline (Visit 2) and Visit 6/EOT/ET (Day 42). 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.

To determine subject eligibility, abnormal Screening clinical laboratory tests may only be repeated after discussion with the Medical Monitor.

11.5.3. 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 by site staff using the equation BMI = weight [kg]/height [m]² at Screening (Visit 1). 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 Screening in vital sign parameters, as determined by the Investigator, will be noted as AEs in the eCRF.

11.5.4. 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.

To determine subject eligibility, the Screening ECG may be repeated in the event of technical difficulty or error associated with the first ECG or if clinically indicated. Subject should rest supine for at least 10 minutes prior to all ECGs.

11.5.5. 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.

All physical examination and neurological examination findings at Screening will be captured in the medical history in the eCRF. Any clinically significant changes from Screening, as determined by the Investigator, will be noted as AEs in the eCRF.

11.5.6. Safety Scales

11.5.6.1. 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 2 versions of the C-SSRS. At the Screening Visit, the Baseline/Screening version will be completed; for all subsequent visits, the "Since Last Visit" version of the C-SSRS will be administered.

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 the C-SSRS assessment at the Screening Visit (in the past 3 months [90 days]) or Baseline are not eligible and must be referred to the Investigator for follow-up evaluation.

If a subject answers "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on any post-Baseline C-SSRS assessment, the subject 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.

11.5.6.2. Young Mania Rating Scale (YMRS)

In addition to administration of the YMRS at Screening and Baseline to determine subject eligibility, the YMRS will be administered post-Baseline as a safety assessment and to inform the identification of treatment-emergent mania or hypomania. See Section 11.3.6 for a description of the YMRS instrument.

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.

11.5.6.3. Abnormal Involuntary Movement Scale (AIMS)

The AIMS will be administered at Baseline and Visit 6 (Day 42). 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.

11.5.6.4. Barnes Akathisia Rating Scale (BARS)

The BARS will be administered at Baseline and Visit 6 (Day 42). 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 (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.

11.5.6.5. Modified Simpson-Angus Scale (SAS)

The modified SAS will be administered at Baseline and Visit 6 (Day 42). 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 of SAS scores, will be provided in the Study Reference Manual.

11.5.6.6. Physician's Withdrawal Checklist (PWC)

Potential withdrawal effects will be assessed by the clinician using the PWC after completion of all scheduled efficacy and safety assessments and procedures at Visit 6 (Day 42) and Visit 7 (Follow-up). 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.

11.6. Pharmacokinetic Assessments

Plasma samples will be collected for population pharmacokinetics (Pop-PK) at Baseline (Visit 2), Visit 4 (Day 14), Visit 6 (Day 42), and Visit 7 (Follow-up). These samples, together with a sample collected at Screening, will also be measured for plasma prolactin levels (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 at Visit 4 (Day 14) and Visit 6 (Day 42) only.

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

Remaining plasma samples after amisulpride PK and prolactin analysis may also be used for the additional characterization and/or bioanalytical method development of putative metabolites of amisulpride and for other exploratory measurements, if needed.

11.7. Pharmacogenomic Testing (Optional)

Subjects will be asked if they are willing to provide a blood sample at Baseline for pharmacogenomic testing. This is optional and requires a separate Informed Consent.

If a subject has consented to have a deoxyribonucleic acid (DNA) sample taken for potential need of genetic analysis (and is eligible for randomization), a blood sample (approximately 4 mL) for potential pharmacogenetic (PGx) analysis will be taken at Baseline prior to dosing on Day 1. Details on collection and shipment will be provided in the Laboratory Investigator Manual. Following shipment, DNA will be extracted and stored safely until further decision on whether an actual genomics testing will be performed is made by the Sponsor. If yes, the timing of the analysis may be following completion of this study and as such will be reported separately. The PGx laboratory will remain blinded to the identity of the subject but will have access to information relating to demographics (ethnic origin and gender). See Section 23, Appendix IV for details, including instructions of PGx sample handling. Samples should not be collected if the subject has not consented to PGx sampling.

11.8. 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.

11.8.1. Screening: Visit 1 (Day -22 to -2)

Subjects will be evaluated at the Screening Visit to determine their eligibility to enroll in the study. This visit should be scheduled as an early morning appointment due to subject recommendation to fast for blood sample collection for clinical laboratory tests.

Hospitalization during the Screening Period will not be allowed, except

- where required by local regulations, or
- when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms.

Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization. In such cases, a maximum of 7 days' hospitalization during washout of prior medications in the Screening Period will be allowed. If an extension is required, medical justification must be provided to the Medical Monitor and the Medical Monitor, following Sponsor review, must approve the request to extend the duration of hospitalization.

To determine subject eligibility, abnormal Screening clinical laboratory tests may only be repeated after discussion with the Medical Monitor.

To determine subject eligibility, the Screening ECG may be repeated in the event of technical difficulty or error associated with the first ECG or if clinically indicated.

The following study-related procedures will be performed at Visit 1; it is suggested that they be performed in the order presented below, as is possible by the site:

- Obtain signed informed consent from the subject before conducting any other visit procedures, including signed informed consent for duplicate subject check (where local regulations allow).
- Obtain signed consent for optional pharmacogenomic sampling (if applicable).
- Administer Lifetime Illness Characteristics Questionnaire.
- Administer MADRS-S. To be eligible for enrollment, subjects must have a MADRS-S total score ≥ 22 (see Section 25, Appendix VI).
- Administer MADRS. To be eligible for enrollment, subjects must have a MADRS total score ≥ 22 (see Section 25, Appendix VI).
- Administer SCID-5-CT.
- Administer YMRS. To be eligible for enrollment, subjects must have a YMRS total score ≤ 12.
- Administer CGI-BP-S.
- Administer C-SSRS (Baseline/Screening version).
- Review inclusion and exclusion criteria.
- Perform duplicate enrollment check (a separate informed consent is required). (see Section 11.1)
- Record demographics.
- Record medical history.
- Record psychiatric history. Note: the psychiatric history includes a psychiatric history form that will include variables related to duration of illness, treatment response (eg, prior medications used to treat bipolar disorder) and other similar variables.
- Record family (eg, biological mother, father, siblings, children) psychiatric and medical history.
- Record prior and concomitant medications.
- Record adverse events (Note: events occurring prior to first dose of study of study drug will be identified programmatically as pretreatment events.)
- Perform physical examination.
- Perform neurological examination.

- Record height and weight.
- Calculate and record BMI.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Collect blood sample(s) for the following clinical laboratory tests (If possible, subjects should fast for at least 8 hours to avoid potential for retest.):
  - Hematology and Serum Chemistry
  - Thyroid Panel
  - Serum Follicle Stimulating Hormone (Female Subjects)
  - Serum β-hCG (Female Subjects of childbearing potential)
  - Serum prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - high sensitivity (hs) C-reactive Protein
- Collect blood sample for Hepatitis B/C testing.
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect urine sample for urine drug screen and urinalysis.
- Perform 12-lead ECG.
- Schedule next visit.
- Approval from the Sponsor Eligibility Committee to proceed to the Baseline Visit is required (Inclusion Criterion 19) (See Section 26, Appendix VII).

11.8.2. Baseline and Treatment Period: Day -1 to Day 42

11.8.2.1. Visit 2: Baseline (Day -1)

Hospitalization at Baseline will not be allowed, except

- where required by local regulations, or
- when determined to be clinically indicated based on the subject's psychiatric history and current psychiatric symptoms.

Medical justification must be provided to the Medical Monitor and the Medical Monitor must approve the request for hospitalization. In such cases, a maximum of 7 days' hospitalization during Week 1 of study medication dosing will be allowed. If an extension is required, medical justification must be provided to the Medical Monitor and the Medical Monitor, following Sponsor review, must approve the request to extend the duration of hospitalization.

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

- Obtained signed consent for optional pharmacogenomic sampling, where applicable (if not done at Screening).
- Review inclusion and exclusion criteria.
- Record prior and concomitant medications.
- Record adverse events. (Note: events occurring prior to first dose of study of study drug will be identified programmatically as pretreatment events.)
- Administer MADRS: To be eligible for enrollment, subjects must have a MADRS total score ≥ 22. Subjects who have a decrease (improvement) of ≥ 25% in MADRS total score from Screening to Baseline, or who have a MADRS total score < 22 at Baseline will not be eligible for enrollment (see Section 25, Appendix VI).
- Administer HAM-A using the SIGH-A.
- Administer YMRS. To be eligible for enrollment, subjects must have a YMRS total score ≤ 12.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer CGI-BP-S.
- Administer C-SSRS (Since Last Visit version).
- Administer AIMS.
- Administer BARS.
- Administer Modified SAS.
- Subject Eligibility Check via IXRS
- Perform physical examination.
- Perform neurological examination.
- Record weight.
- Record waist circumference.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.):
  - Hematology and Serum Chemistry
  - Thyroid Panel

  - Serum prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - hs C-Reactive Protein
- Collect blood sample for measurement of plasma concentrations of aramisulpride, esamisulpride, and prolactin.
- Collect blood sample for pharmacogenomic testing (subjects signing a separate informed consent).
- Collect urine sample for rapid urine drug test, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Perform 12-lead ECG.
- Randomize subject.
- Dispense study drug.
  - Instruct subject to administer a single oral dose of study medication approximately the same time each day at home beginning the following morning (Day 1).
- Schedule next visit:
  - Instruct subject to take the morning dose prior to the next clinic visit. Clinic visits are to begin no later than 6 hours postdose, if possible.
  - Instruct subject to record date and time of the last 3 doses prior to next visit and bring back all used/unused study drug and packaging to the next visit.

11.8.2.2. Visit 3 (Day 7 ± 2)

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

- Administer MADRS.
- Administer HAM-A using the SIGH-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS (Since Last Visit version).
- Record prior and concomitant medications.
- Record adverse events.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Perform 12-lead ECG.

- Perform study drug accountability.
  - Collect used/unused study drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source.
- 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 take 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 date and time of the last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.

11.8.2.3. Visits 4 (Day 14 ± 2)

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

- Administer MADRS.
- Administer HAM-A using the SIGH-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS (Since Last Visit version).
- Record prior and concomitant medications.
- Record adverse events.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Perform 12-lead ECG.
- Collect blood sample(s) for the following clinical laboratory tests:
  - Hematology and Serum Chemistry
  - Serum prolactin
- 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 study drug accountability.
  - Collect used/unused study 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 record date and time of the last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to next visit.

11.8.2.4. Telephone Contact (Day 21 ± 2)

The clinical site will contact subjects by telephone on Day 21 (± 2) to assess adverse events and concomitant medications. The clinical site will remind the subject of their next scheduled visit and to continue once daily dosing with study drug and remind subject to administer the morning dose prior to the next clinic visit.

11.8.2.5. Visit 5 (Day 28 ± 2)

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

- Administer MADRS.
- Administer HAM-A using the SIGH-A.
- Administer YMRS.
- Administer CGI-BP-S.
- Administer C-SSRS (since last visit version).
- Record prior and concomitant medications.
- Record adverse events.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Perform 12-lead ECG.
- Perform study drug accountability.
  - Collect used/unused study drug and packaging.
  - Confirm with the subject the date and time of their last 3 doses of study drug and record in the source.
- 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 date and time of the last 3 doses prior to next visit and to bring back all used/unused study drug and packaging to the next visit.

11.8.2.6. Telephone Contact: (Day 35 ± 2)

The clinical site will contact subjects by telephone on Day 35 (± 2) to assess adverse events and concomitant medications. The clinical site will remind the subject of their next scheduled visit and to continue once daily dosing with study drug and remind subject to administer the morning dose prior to the next clinic visit.

11.8.3. Visit 6: End of Treatment/Early Termination (Day 42 ± 2)

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

- Administer MADRS.
- Administer HAM-A using the SIGH-A.
- Administer YMRS.
- Administer PWC.
- Administer QIDS-SR16.
- Administer SDS.
- Administer EQ-5D-5L.
- Administer SHAPS.
- Administer CGI-BP-S.
- Administer C-SSRS (Since Last Visit version).
- Administer AIMS.
- Administer BARS.
- Administer Modified SAS.
- Perform physical examination.
- Perform neurological examination.
- Record weight.
- Record waist circumference.
- Record prior and concomitant medications.
- Record adverse events.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.

- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours.):
  - Hematology and Serum Chemistry
  - Thyroid Panel
  - Serum prolactin
  - HbA1c
  - Lipid Panel
  - Serum Insulin
  - hs C-reactive Protein
- 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 study 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.

At this visit, subjects who have participated throughout the duration of the Treatment Period, up to and including Visit 6 (Day 42) will have the option to enroll and continue treatment in an open-label safety extension study (SEP380-303). Subjects who provide consent to participate in the extension study and meet the study entry criteria will not need to return for further visits in this study.

A Follow-up Visit will be scheduled for subjects who do not enter the extension study.

11.8.4. Follow-up: Visit 7 (7 ± 2 days after last dose)

All subjects who discontinue early or do not enroll in the open-label safety extension study (Study SEP380-303) will have a safety Follow-up Visit 7 ± 2 days after their last dose of study drug. The following study-related procedures will be performed at Visit 7; 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 (Since Last Visit version).
- Record prior and concomitant medications.
- Record adverse events.
- Perform physical examination.

- Perform neurological examination.
- Record weight.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Perform 12-lead ECG.
- Collect blood sample(s) for the following clinical laboratory tests:
  - Hematology and Serum Chemistry
  - Serum prolactin
- 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).

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

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

Untoward medical occurrences that occur between the time of signing the informed consent form (ICF) and drug administration are pretreatment events. Those that occur after administration of study drug are considered AEs. Pretreatment hospitalizations that occur in accordance with local clinical practice during the Screening Period (for wash-out from prior or concomitant medications) will not be considered SAEs and do not need to be reported as such. Any untoward event that may occur during the hospitalization must be recorded as a pretreatment event. If hospitalization is prolonged by an untoward event, the event must be reported as an SAE.

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

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

12.1.2. Serious Adverse Events

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

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- 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 a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

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

SAE criteria information will be captured on the 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.

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. Adverse events of special interest 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.

A subject who develops an AE of amenorrhea, gynecomastia, or galactorrhea must be discontinued from the study, referred to the Investigator for follow-up evaluation, and followed until the event resolves (see Section 13.1).

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, vital signs, and physical or neurological examination observation) occurring after the Screening Visit 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. If the result of any test (or repeat test, if done) from the samples taken during Screening is indicated as clinically significant and is not covered by the inclusion criteria in Section 8.1, the subject will **not** be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in any clinical laboratory test, ECG value, vital sign measurement, or physical or neurological examination observation after dosing, during the study, and/or at the Follow-Up Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized.

12.3. Collection and Recording of Adverse Events

All pretreatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. Pretreatment events and AEs and SAEs that occur from the signing of informed consent to the subject's last study visit must be recorded on the eCRF. Determination of whether an event is a pretreatment event, or an adverse event will be made programmatically by the Sponsor or designee, not by the site.

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 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/serious pretreatment event
- 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/Serious Pretreatment 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. Serious pretreatment events must be reported on the SAE form and recorded on the CRF, in the same manner as SAEs.

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 a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the 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 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 DSMB may review blinded, unblinded, or partially unblinded data, but the Sponsor (with the exception of the relevant members of the pharmacovigilance team responsible for reporting Suspected Unexpected Serious Adverse Reactions [SUSARs]), the CRO, and the Investigators will remain blinded until the official unblinding of the database. 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, gynecomastia, or galactorrhea 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 even 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 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 6 (Day 42) will undergo procedures and assessments scheduled for Visit 6 (Day 42) at the time of early discontinuation (see Section 11.8.3).

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 11.8.3 and safety Follow-up Visit described in Section 11.8.4.

15. STATISTICS

15.1. Sample Size

The sample size is estimated based on the primary efficacy endpoint, the change from Baseline in MADRS total score at Week 6. Based on the Phase 2 Study SEP380-201 results for both planned and post-hoc analyses of the primary endpoint, assuming a common standard deviation (SD) of 10 and a mean improvement of 3.5 (effect size 0.35) and 3.5 (effect size 0.35) over placebo for SEP-4199 200 mg and 400 mg dose groups, respectively, with a randomization ratio of 1:1:1 for placebo, SEP-4199 200 mg and 400 mg, a sample size of 165 subjects per treatment group will provide at least 80% conjunctive power to reject both null hypotheses of no difference between SEP-4199 doses and placebo and at least 85% power to reject each individual null hypothesis after multiplicity adjustment for two comparisons of the primary endpoint using the enhanced mixture truncated Hochberg gatekeeping procedure (Kordzakhia 2018) with truncation parameter 0.5 and 2-sided Type I error of 0.05. An upward adjustment of approximately 5% is assumed to compensate for subjects who are randomized but have no post-Baseline efficacy assessment. Thus, a total sample of approximately 174 subjects per group (522 subjects in total) will be randomized. The sample size calculation is based Monte Carlo computer simulations.

15.2. Statistical Hypotheses

The hypotheses associated with the primary and secondary efficacy endpoints will be tested using a testing procedure described in Section 15.4.3.4.

Primary Hypotheses

In adults with moderate-to-severe symptoms of depression, after 6 weeks of treatment,

- SEP-4199 CR 200 mg/day leads to greater reductions from Baseline in MADRS total score at Week 6 relative to placebo
- SEP-4199 CR 400 mg/day leads to greater reductions from Baseline in MADRS total score at Week 6 relative to placebo

Secondary Hypotheses

In adults with moderate-to-severe symptoms of depression, after 6 weeks of treatment,

- SEP-4199 CR 200 mg/day leads to greater reductions from Baseline in CGI-BP-S depression score at Week 6 relative to placebo
- SEP-4199 CR 400 mg/day leads to greater reduction from Baseline in CGI-BP-S depression score at Week 6 relative to placebo

15.3. Analysis Populations

Intention-to-Treat Population: The intention-to-treat (ITT) population will consist of subjects who are randomized who received at least one dose of study medication and have at least one post-Baseline assessment in any efficacy variable. The ITT population is the primary population for efficacy analyses, ie, unless otherwise specified, all efficacy analyses will be based on the ITT population. Subjects in the ITT population will be analyzed based on the treatment to which they are randomized.

Per Protocol Population: The Per Protocol (PP) population will consist of all ITT subjects who have no major protocol deviations that may affect the interpretation of the primary efficacy endpoint defined in Section 15.4.2. Subjects in the Per Protocol population will be analyzed according to their randomized treatment group.

Primary analysis of the primary and the secondary efficacy endpoints will also be performed using the Per Protocol population.

Safety Population: The safety population will consist of all subjects who randomized and receive at least one dose of study medication. Subjects will be analyzed according to modal dose (the predominant treatment, used interchangeably) received. The modal dose or predominant treatment is defined as the treatment to which the subject is exposed for the greatest duration during the treatment period. This will generally be the same as the randomized treatment group, unless the subject takes incorrect study medication during their entire participation in the study.

Follow-up Population: The follow-up population includes all randomized subjects who receive at least one dose of study medication, and either discontinue the study drug during the treatment period before the Week 6 visit or complete the 6-week treatment period but do not enter the extension study (Study SEP380-303), and have at least one assessment after the double-blind Treatment Period for any safety evaluation. The follow-up population will be mainly used to summarize a few selected safety assessments (ie, AE, ECG, Lab, Vital Signs, PWC score) which have a follow-up assessment.

Pharmacokinetic (PK) Population: The PK population includes all subjects who are randomized, receive at least 1 dose of study drug, and have any post-Baseline PK concentrations of SEP-4199. PK samples collected from placebo subjects will not be analyzed.

The PK analysis will be based on the PK population.

Population PK (Pop-PK) analysis methods will be used to characterize the PK/PD profiles in subjects treated with SEP-4199. These methods will be described in a separate document and will not be included in the SAP.

15.4. Data Analysis

All statistical inference analyses will be performed with 2-sided tests at a significance level of 0.05, and 2-sided 95% confidence intervals (CI) will be calculated whenever appropriate. All data will be summarized by treatment group and visit as appropriate. All subject data will be presented in data listings by subject.

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, prior and concomitant medication, and the important protocol deviations, will be presented by treatment group, and overall for both the ITT and the Safety population. Details of the summary approaches for subject level information will be provided in the SAP and no further discussion is provided hereafter in this document.

15.4.2. Per Protocol Criteria

Protocol violator criteria used to define the Per Protocol population may include, but will not be limited to the following:

- Subject received incorrect study treatment or was not dosed in double-blind treatment period.
- Subject does not have a Baseline efficacy measurement or at least one post-Baseline efficacy measurement for primary efficacy variable.
- Subject was unblinded during the double-blind treatment period.
- Subject does not have 14 days or more of drug exposure.
- Subject had < 75% or > 125% non-missing medication compliance or missing medication compliance unless the overall drug compliance per the worst-case imputation is ≥ 75% and ≤ 125%.
- Subject violated inclusion/exclusion criteria which have any potential impact on efficacy results (confirmed by medical review).
- Subject took a prohibited medication or more than one day of a prohibited dose of an allowed medication or received prohibited psychotherapy during the double-blind treatment period that would impact the primary efficacy analysis (confirmed by medical review).
- If subject tests positive for substance abuse at post-Baseline during the double-blind treatment period, without a verified prescription for use of a drug that potentially could have caused the positive test result (confirmed by medical review).

A complete list of subjects who meet at least one of above protocol deviations criteria, will be identified through a blinded data review meeting (BDRM) prior to database lock. Subjects in the ITT population regarded as protocol deviators per above criteria will not be included in the PP population.

15.4.3. Efficacy Analyses

The primary analysis population for the efficacy analysis will be ITT population. Assessment of the primary and secondary efficacy endpoints on the PP population will be conducted as supportive analyses.

Multiplicity adjustment to control the global familywise Type I error rate for testing SEP-4199 CR 200 mg versus placebo and SEP-4199 CR 400 mg versus placebo across the primary and secondary efficacy endpoints at the 5% level is described in Section 15.4.3.4.

Whenever mixed model for repeated measures (MMRM) or analysis of covariance (ANCOVA) analyses are conducted, LS mean of treatment difference, associated 95% confidence interval (CI), and p-value (nominal) will be generated per corresponding statistical model. For each efficacy variable, effect sizes for within-group and between-group at each post-Baseline visit will be provided.

For total and subscale scale scores of all efficacy variables (continuous), and for individual item scores of selected efficacy variables (MADRS, HAM-A, YMRS, etc.), summary statistics (N,

mean, standard deviation, median, first quartile [Q1], third quartile [Q3], and range) will be presented at each assessment time point for the actual values and the changes from Baseline, and 95% CIs of the changes from Baseline will also be presented by treatment.

15.4.3.1. Primary Efficacy Endpoint Analysis

The estimand of primary interest is described below:

Population of Interest	Adults who meet inclusion/exclusion criteria (major depressive episode associated with bipolar I disorder and have moderate-to-severe symptoms of depression as demonstrated by a MADRS total score ≥ 22 and CGI-BP-S depression score ≥ 4 at Screening and Baseline) and be in the ITT population.
Outcome Measure/ Endpoint	Change from Baseline in MADRS total score at Week 6.
Treatment Condition of Interest	A hypothetical strategy is used to address intercurrent event, assuming that the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.
Intercurrent Event	Regardless of adherence to treatment (ie, discontinuation of assigned treatment)
Population-Level Summary Measure	Treatment difference between SEP-4199 CR dose groups and placebo for mean change from Baseline in MADRS total score by using the mixed model for repeated measures (MMRM) per the randomized treatment based on the ITT population.

The primary efficacy analyses of the primary efficacy endpoint (the change from Baseline in MADRS total score at Week 6) will be performed using a likelihood-based MMRM model based on the ITT population. The response (dependent) variable is the change from Baseline in the MADRS total score assessed at Weeks 1, 2, 4, and 6. Specifically, the MMRM model includes fixed effects terms for treatment, visit (as a categorical variable), pooled country, Baseline MADRS total score, and treatment-by-visit interaction. Restricted maximum likelihood estimation method will be applied using an unstructured covariance model. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. The least squares (LS) mean treatment differences (each SEP-4199 CR dose minus placebo) of change from Baseline at Week 6, 2-sided 95% confidence intervals (CI), and the associated p-values will be calculated based on this model.

Multiplicity adjustment to control the global familywise Type I error rate at 5% is described in Section 15.4.3.4.

The model assumptions underlying the primary analysis will be assessed. Specifically, the normality and homoscedasticity assumptions underlying the primary MMRM model will be assessed graphically. Conditional studentized and scaled residuals will be plotted against the predicted values, respectively, and Q-Q (quantile-quantile) plots of these residuals versus the expected quantiles of the standard normal distribution will be presented to provide a graphical view of similarity and difference in the two distributions. If the unstructured covariance model fails to converge, a more parsimonious model is likely necessary, but not necessarily correct. In

this case, MMRM based on structures more general than unstructured one, ie, separate unstructured matrices by treatment, will be checked. For rare chance, if such model fails again, a more parsimonious model (eg, spatial exponential covariance pattern) may be assessed as necessary. If there is evidence of deviations from the model assumption(s), the degree and nature of such deviation(s) will be explored to better understand the potential impact on interpretation of the primary efficacy analysis.

15.4.3.1.1. Sensitivity Analyses

To address early dropouts under the assumption of missing not at random (MNAR), a pattern-mixture model using a placebo-based multiple imputation method and a pattern mixture model using multiple imputations with penalties (ie, deflating the individually estimated treatment effect size by known factors) will be performed as sensitivity analyses to explore the robustness of the MMRM results for the primary analysis. In case of a deviation from the assumptions required for the primary analysis, to confirm the robustness of the primary analysis result, additional sensitivity analysis per permutation test will be performed: fit a large number of datasets based on a same MMRM for the primary analysis with randomly assigning pseudo-treatment group designations.

15.4.3.1.2. Supportive Analyses

The primary efficacy endpoint will also be analyzed using an ANCOVA model using the LOCF approach, as a supportive analysis. The model will include terms for treatment, pooled country, and Baseline MADRS total score as covariates.

The primary efficacy analysis will be repeated for the PP population to examine the impact of protocol violation and deviations in a way that is less biased and to obtain a more interpretable result.

15.4.3.1.3. Additional Analyses for Regional Effect

To support global regulatory decision-making, the consistency of treatment effects across regions (ie, North America, Latin America, Europe, Japan) will be assessed. Treatment effects and measures of their uncertainty for individual region, and treatment-by-region interaction will be evaluated for the primary efficacy endpoint. An MMRM model that includes fixed effects terms for treatment, visit (as a categorical variable), region, Baseline MADRS total score, treatment*visit interaction, treatment*region interaction, and treatment*visit*region interaction, will be performed using an unstructured covariance matrix. If p-value for treatment-by-region interaction at Week 6 is significant at level of 0.10, the nature of this significant interaction (quantitative vs qualitative) will be further evaluated using the Gail and Simon test (Gail 1985) and other interaction tests such as the Pan-Wolfe test (Pan 1997). The Gail and Simon test tends to perform better when there are several subgroups with effects which are positive and several also with effects which are negative while the Pan and Wolfe tends to perform better if the effects in most of the subgroups are in one direction and there are only one or very few subgroups for which the effect is in the opposite direction. Shrinkage analyses for treatment effect of regions, which are based on weighted averages of the overall effect estimate and the estimate using data from individual regions, will be performed. Shrinkage analyses for treatment effect of countries may be performed, as appropriate.

15.4.3.2. Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoint (change from Baseline in CGI-BP-S depression score at Week 6) will be analyzed with an MMRM model similar to the one used in the primary efficacy analysis (adjusted with the corresponding Baseline). The LS mean treatment differences (each SEP-4199 CR dose minus placebo) of change from Baseline at Week 6, their 2-sided 95% CIs, and the associated p-values will be calculated based on the model. Additional supportive and sensitivity analyses similar to the ones performed for the primary efficacy endpoint will be conducted for the secondary efficacy endpoint to address early dropouts or potential deviations from the model assumption(s).

Multiplicity adjustment to control the global familywise Type I error rate at 5% is described in Section 15.4.3.4.

15.4.3.3. Additional Efficacy Endpoint Analyses

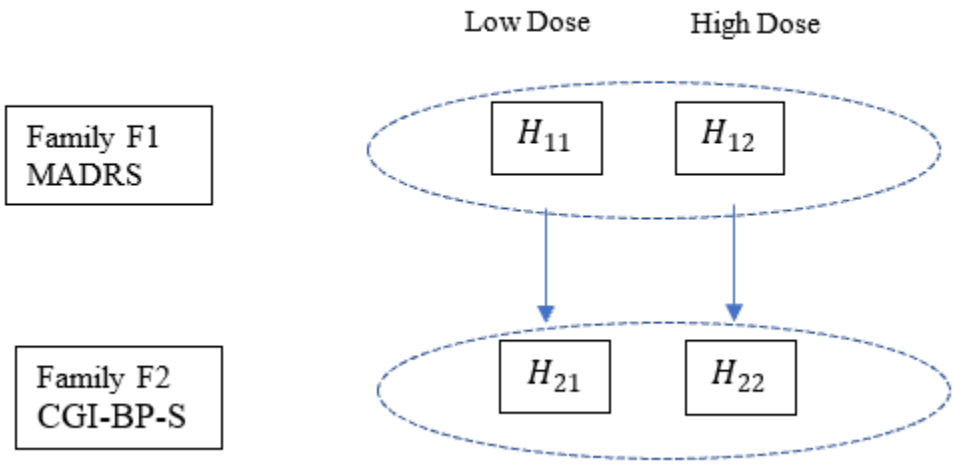
MADRS-6 core symptoms subscale score and HAM-A total score will be analyzed with an MMRM model similar to the one used in the primary efficacy analysis adjusted with the corresponding Baseline. QIDS-SR16 total score, SDS total score and subscale scores, EQ-5D-5L related scores, and SHAPS total score will be analyzed with an ANCOVA model similar to the one used in the supportive ANCOVA analysis for the primary efficacy endpoint adjusted with the corresponding Baseline as covariate.

Categorical efficacy endpoints (ie, proportion of responders and proportion of remitters at Week 6) will be analyzed using a logistic regression model with treatment, region, and Baseline MADRS total score as covariates using a LOCF approach. Proportion of subjects meeting functional remission criteria per the SDS subscales (defined as SDS total score ≤ 6 and SDS subscale scores ≤ 2) will be analyzed using a similar logistic regression model with corresponding Baseline as covariate.

15.4.3.4. Adjustment for Multiplicity

The hypotheses associated with the primary and secondary variables for efficacy claim are grouped into 2 hierarchical families: Families 1 and 2, respectively. The enhanced mixture truncated Hochberg-based gatekeeping procedure with the logical relationships among the hypotheses (ie, H_{21} will be tested only if H_{11} is rejected; H_{22} will be tested only if H_{12} is rejected) will be applied to control the family-wise Type 1 error rate of 5% (two-sided) for the hypotheses in Families 1 and 2. The truncation parameter in Family 1, which is used to determine α propagation rule, is chosen as 0.5. The details for how to generate corresponding adjusted p-value for individual hypothesis based on above multiplicity adjustment approach will be provided in the SAP.

Figure 2: Hierarchy of Hypothesis Testing for Primary and Secondary Efficacy Endpoints



Choice of Truncation Parameter γ per Power Simulation for Sample Size Calculation

Assessment of the procedure's power facilitates the selection of the truncation parameter γ. The truncation parameter γ determines the balance of power between Families 1 and 2. Due to the testing logical restriction, power of H_{21} will be less than that of H_{11} and power of H_{22} will be less than that of H_{12}. Various types of power of the truncated Hochberg-based gatekeeping procedure can be evaluated via simulations. Power simulations were performed using the parameter settings below and other scenarios were also performed to further evaluate the robustness of power profile when deviation from the initial assumption of effect size occurs.

Correlation ρ	Simulation Case	Effect Size			
		MADRS Total Score		CGI-BP-S Depression Score	
		Low Dose	High Dose	Low Dose	High Dose
0.7	Case 1	0.35	0.35	0.35	0.35
	Case 2	0.35	0.35	0.33	0.33

Simulation parameters for power: N=165/Arm, 100,000 simulations.

Details of the simulation results, including both conjunctive power (rejecting both hypotheses within a family) and disjunctive power (rejecting at least one null hypothesis within a family) for Family 1 and Family 2 will be provided in the SAP. The key simulation results are summarized here: under the parameter settings, both conjunctive and disjunctive powers for Family 1 are very stable regardless of choice of the truncation parameter; on the contrary, disjunctive power for Family 2 showed a clear variation pending on selection of the truncation parameter. It is important to point out that the Hochberg-based truncated gatekeeping procedure does not make any assumption about the correlation among the two endpoints.

15.4.3.5. Efficacy Subgroup Analysis

The primary efficacy variable (change from Baseline in MADRS total score at Week 6) and secondary efficacy variable (change from Baseline in CGI-BP-S depression score at Week 6) will be examined to explore the consistency of the treatment effect across certain subgroups at Week 6. Subgroups, including but not limited to gender, race, region, and country (pooled), will be detailed in the SAP. For each subgroup except region and country, a subgroup analysis will be conducted on an MMRM model similar to the one used in the corresponding primary efficacy analysis with 3 additional terms: subgroup, treatment-by-subgroup interaction, and 3-way interaction of treatment*subgroup*visit. For country, a subgroup analysis will be conducted on an MMRM model similar to the one used in the corresponding primary efficacy analysis with 2 additional terms: treatment-by-subgroup interaction, and 3-way interaction of treatment*subgroup*visit. For region, a similar MMRM subgroup analysis as for 'country' will be performed by replacing 'country' by 'region'. Based on the above analysis models, LS mean treatment differences (each SEP-4199 CR dose group vs. placebo) at Week 6, corresponding 2-sided 95% CIs for each subgroup level, and p-value of treatment-by-subgroup interaction at Week 6 will be generated. Summary statistics by treatment group within each subgroup level will be provided as well.

15.4.4. Safety Analyses

Unless otherwise specified, the safety data analysis will be based on the Safety population. For a few selected safety assessments (AE, ECG, Lab, Vital Signs), additional summaries will be provided per the follow-up population as well, as appropriate.

15.4.4.1. Adverse Events

All AEs will be coded using MedDRA. Information on the format and version of coding dictionary is provided in the DMP. A treatment-emergent adverse event (hereafter referred to as AE) is defined as an untoward medical event with a start date on or after the date of the first dose of study drug through 7 days after study drug discontinuation (14 days for SAEs) for subjects who complete or discontinue this study but do not enter into the extension study), or through the last study day of the double-blind treatment period for subjects continuing into the extension study.

The overall incidence (ie, number and percentage of subjects with one or more AEs in each category) of AEs, discontinuation due to AEs, and SAEs will be summarized by treatment group.

The AEs also will be summarized by system organ class (SOC) and preferred term (PT) by presenting the number and percentage of subjects with each AE category. The incidence of AEs (by PT, grouped by SOC, and presented by treatment group) also will 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 be also 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 hyperprolactinemia-related AEs, will be summarized by treatment group for overall and by gender as appropriate. AEs associated with EPS will be summarized by treatment 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 by SOC and PT separately for subjects in the Follow-up population.

15.4.4.2. Treatment-Emergent Mania and YMRS

Treatment-emergent mania is defined as a YMRS score ≥ 16 on any 2 consecutive post-Baseline visits or at the final assessment, or an AE of mania or hypomania. If a subject has no reported AE of mania or hypomania and has no post-Baseline assessment of YMRS, incidence of treatment-emergent mania will be set to missing. SEP-4199 CR will be compared to placebo in incidence of treatment-emergent mania in a logistic regression model including factors of treatment, region, and Baseline YMRS total score covariate.

The change from Baseline in YMRS total score will also be analyzed using the MMRM method described above for the primary efficacy variable and appropriate Baseline as a covariate.

15.4.4.3. Clinical Laboratory Assessments

Descriptive statistics (mean, median, etc) will be provided by visit and treatment group for observed values or changes from Baseline for safety variables (continuous). Categorical results (eg, urinalysis tests) will be summarized by study visit and treatment group using frequency and percentage. Results for glucose, insulin, HOMA-IR, and lipid tests will be presented separately by fasting status, which includes fasting only, and overall (fasting, non-fasting, or unknown). Prolactin values will be summarized by treatment group and gender (male, female, and overall).

In addition, the change from Baseline at endpoint for selected laboratory parameters (eg, HbA1c, insulin, HOMA-IR, glucose, lipids parameters, prolactin) will be evaluated using a nonparametric rank ANCOVA analysis. For comparison versus placebo, stratified by region, the change from Baseline at endpoint and Baseline value will be ranked. A linear regression will be conducted by region, on the change from Baseline ranks and Baseline value rank as independent variable to produce regression residuals. Using the values of the residuals as scores, Mantel-Haenszel row mean score tests will be produced for each SEP-4199 CR dose group versus placebo after stratification by region.

Laboratory data will be summarized by presenting descriptive statistics of shift tables. Number and percentage of subjects with potentially clinically significant (PCS) post-Baseline laboratory value for selected parameters will be summarized by treatment, and by study visit and for assessment period (the SAP will provide details of laboratory PCS criteria).

15.4.4.4. ECGs

Standard 12-lead ECG parameters HR, PR interval, RR interval, QT interval, Bazett's corrected QT (QTcB) and Fridericia's corrected QT (QTcF) intervals, and QRS duration will be assessed. Results of each ECG parameter and their changes from Baseline will be summarized by visit using descriptive statistics.

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 and < 60 msec, and ≥ 60 msec will be summarized by treatment group. Number and percentage of subjects with PCS post-baseline

ECG values will be summarized by treatment, by study visit, and for assessment period (the SAP will provide details of ECG PCS criteria).

15.4.4.5. Vital Signs

Descriptive statistics (mean, median etc.) of the following parameters will be summarized by study visit for actual value as well as change from Baseline (including percent change of body weight) for each treatment 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 treatment group.

An ANCOVA model using the LOCF approach will be conducted for changes from Baseline at Week 6 in change and percent change from Baseline in body weight (kg), and change from Baseline in BMI (kg/m^2). The ANCOVA model will include terms for treatment, region, and corresponding Baseline value as covariate.

Number and percentage of subjects with PCS post-Baseline vital sign values will be summarized by treatment, by study visit, and for assessment period. Number and percentage of subjects with orthostatic hypotension and/or orthostatic tachycardia will be summarized similarly (the SAP will provide details of vital signs PCS Criteria).

15.4.4.6. Movement Disorder Measures

An ANCOVA model using the LOCF approach will be conducted for changes from Baseline at Week 6 in BARS total score, AIMS total score, and SAS 10-item mean score. The ANCOVA model will include terms for treatment, region, and corresponding Baseline value as covariate. LS means for each treatment group, the LS mean of treatment difference (SEP-4199 CR group minus placebo) and the associated two-sided 95% CI will be presented at Week 6. Summary statistics for the observed and change from 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 as well.

Shifts from 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 treatment group, respectively. Details for definition of these classifications will be provided in the SAP.

15.4.4.7. 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 treatment group for the overall post-Baseline treatment period.

15.4.4.8. Physician's Withdrawal Checklist (PWC)

The PWC score will be summarized by presenting descriptive statistics of observed values and changes from Week 6 (Day 42) by treatment group for the follow-up period. Numbers and percentages of subjects with any new symptom or worsened old symptom for any PWC score or each individual symptom score will be also provided.

15.4.5. Pharmacokinetic Analysis

All PK analysis (except of plasma prolactin concentration) will be performed using the PK population. The plasma prolactin concentration will be summarized based on the Safety population in order to display summary statistics for placebo plasma prolactin data.

Any plasma concentration summary statistics below the limit of quantification will be represented by "BLQ". Concentrations at each scheduled sample collection time point will be summarized descriptively (n, mean, SD, median, range, coefficient of variation [CV%], geometric mean, and geometric CV%).

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

15.4.6. Interim Analysis

No interim analysis is planned.

15.4.7. 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 Screening and data collected during the study (except clinical laboratory test results, ECG results, Pop-PK, pharmacogenomic testing, and scales) will be recorded in the subject's eCRF. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulations (CFR) Part 11 (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
Informed consent for optional pharmacogenomic sampling	A
Lifetime Illness Characteristics Questionnaire	C
Montgomery-Asberg Depression Rating Scale, Self-rating Version (MADRS-S)	C
Inclusion/Exclusion Criteria Review	A
Demographics	A
Medical History	A
Psychiatric History	A
Family Psychiatric and Medical History	A
Structured Clinical Interview for DSM 5 Clinical Trial Version (SCID-5-CT)	C
Physical Examination	A
Neurological Examination	A
Prior/Concomitant Medications	A
Subject Eligibility Check	B
Randomization	B

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

Protocol Step	Computerized System Type or Description
Study Drug Accountability	A/B
Dispense Study Drug	B
Administer Study Drug	A
Montgomery-Asberg Depression Rating Scale (MADRS)	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 Dimension – 5 Level (EQ-5D-5L)	C
Snaith-Hamilton Pleasure Scale (SHAPS)	C
Clinical Global Impression – Bipolar Version-Severity of Illness (CGI-BP-S)	C
Vital Signs	A
Height	A
Weight (Including Body Mass Index)	A
Waist Circumference	A
Pretreatment and Adverse Event Monitoring	A
12-Lead Electrocardiogram (ECG)	E
Hematology, Serum Chemistry, and Urinalysis	D
Serum Prolactin	D
Hemoglobin A1c (HbA1c)	D
Lipid Panel	D
Serum Insulin	D
High Sensitivity C-reactive Protein	D
Hepatitis B/C	D
Thyroid Panel	D
Serum Follicle Stimulating Hormone (Female Subjects)	D
Serum β-hCG (Female Subjects of child-bearing potential)	D
Urine β-hCG (Female Subjects of child-bearing potential)	A
Urine Drug Screen	D
Rapid Urine Drug Test	A
Young Mania Rating Scale (YMRS)	C
Physician's Withdrawal Checklist (PWC)	C
Columbia-Suicide Severity Rating Scale (C-SSRS)	C
Abnormal Involuntary Movement Scale (AIMS)	C
Barnes Akathisia Rating Scale (BARS)	C

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

Protocol Step	Computerized System Type or Description
Modified Simpson-Angus Scale (SAS)	C
Blood sample for aramisulpride and esamisulpride PK and Plasma Prolactin	F
Optional Blood Sampling for Pharmacogenomic Testing	F
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 International Council on Harmonization (ICH) Good Clinical Practice (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 handwritten or computer-generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign-in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary, and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.6. Clinical Laboratory Certification and Normal Values

A 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 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 and 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 IRBIEC 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, ICF 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 Investigational New Drug (IND) or ICH GCP, as applicable.

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

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

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported 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 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 the 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 AE 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.

Aitkin CB, Weisler RH, Sachs GS. The Bipolarity index: a clinician-rated measure of diagnostic confidence. Journal of Affective Disorders. 2015;177(59-64).

American Psychiatric Association (APA) Practice guideline for the treatment of patient with bipolar disorder (revision). Am J Psychiatry. 2002;159(4) suppl:1-50.

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.

Fantino B, Moore N. The self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in Major Depressive Disorder. BMC Psychiatry. 2009; 9(26):1-6.

First MB, Williams JBW, Karg RS, Spitzer RL: Structured Clinical Interview for DSM-5—Clinical Trials Version (SCID-5-CT); Arlington, VA, American Psychiatric Association, 2015.

Gail MH, Simon R. Tests for Qualitative Interactions between Treatment Effects and Patient Subsets. Biometrics. 1985; 41:361-372.

Ghaemi SN, Ostacher MM, El-Mallakh RS, Borrelli D, Baldassano CF, Kelly ME, et. al. Antidepressant discontinuation in bipolar depression: A Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry. 2010;71(4):372-80.

Goldberg JF, Brooks JO 3rd, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, et. al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder; findings from the STEP-BD. J Clin Psychiatry. 2009:70(2):155-62.

Gutierrez-Rojas L, Gurpegui M., Ayuso-Mateos JL, Gutierrez-Ariza JA, Ruiz-Veguilla M, Jurado D. Quality of life in bipolar disorder patients: a comparison with a general population sample. Bipolar Disord. 2008:10(5):625-34.

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.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59:530-7.

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser J, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003;60:261-9.

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

Kordzakhia G, Brechenmacher T, Ishida E, Dmitrienko A, Zheng WW, Li DF. An enhanced mixture method for constructing gatekeeping procedures in clinical trials. Journal of Biopharmaceutical Statistics. 2018;28(1):113-128.

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.

Magalhaes PV, Kapczinski F, Nierenberg AA, Dackersbach T, Weisinger D, Dodd S, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand. 2012;125(4):303-8.

Merikangas KR, Akiskal HS, Angst J, Greenberg MA, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of General Psychiatry. 2007;64:543-52.

Miller S, Dell'Osso B, Ketter TA. The prevalence and burden of bipolar depression. J Affect Disord. 2014 Dec;169 Suppl 1:S3-S11.

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

Mundt JC, Katzelnick DJ, Kennedy SH, Eisfeld BS, Bouffard BB, Greist JH. Validation of an IVRS version of the MADRS. J Psychiatr Res. 2006 Apr; 40(3):242-6.

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

Pan G, Wolfe DA. Test for qualitative interaction of clinical significance. Statistics in Medicine. 1997; 16(14):1645-1652.

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

Shippee ND, Shah ND, Williams MD, Moriarty JP, Frye MA, Ziegenfuss JY. Differences in demographic composition and in work, social, and functional limitations among the populations with unipolar depression and bipolar disorder: results from a nationally representative sample. Health Qual Life Outcomes. 2011;9:90.

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, SEP380-301, Version 3.00, "A Multi-region, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating 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), Alkaline Phosphatase (ALP), Albumin, 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, LDL-Cholesterol, 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

SEROLOGY PANEL: Hepatitis B Ag and Hepatitis C Ab

RENAL FUNCTIONING: Creatinine clearance (Calculated GFR)

OTHER TESTS: Follicle-stimulating Hormone (FSH; postmenopausal women or if menopause is suspected; Screening visit only), 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.	Day No.	Aramisulpride and Esamisulpride PK and Plasma Prolactin Blood Sample Collection Times:
1	-22 to -2	Baseline prolactin only
2	-1	Predose for PK and prolactin
4	14 (± 2)	Postdose* for PK and prolactin
6	42 (± 2)	Postdose* for PK and prolactin
7	7 (± 2) days after last dose	Follow-up**for PK and prolactin

* 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. PHARMACOGENOMICS SAMPLE COLLECTON AND HANDLING GUIDELINE

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

BLOOD SAMPLES FOR POTENTIAL PHARMACOGENOMICS

- A blood sample (approximately 4.0 mL) will be collected at Baseline (Visit 2) using a 4 mL Vacutainer® (or equivalent) collection tube containing K2-EDTA as an anticoagulant.
- The tubes containing blood samples will be labeled with the following information: unique barcode (if possible), protocol number, subject number, and sample date of collection.
- Blood samples will be kept upright on wet ice upon blood draw and will be stored frozen at approximately -70°C within 10 min of collection until shipment to the appropriate laboratory. For sites without a -70°C freezer, samples should be shipped to the central laboratory within 24 hours of collection (prior to shipping, must be stored frozen at -20°C).
- The blood samples for pharmacogenomics will be shipped in leak proof double-plastic sealed bags with approximately 20 pounds of dry ice placed in insulated shipping containers labeled on the outside with “Human Specimens/Non-infectious”. Packing material such as bubble wrap or other cushioning material will be placed around the samples to prevent breakage during shipping. Samples will be shipped in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.
- The shipping details will be defined in the Laboratory Investigator Manual.

24. APPENDIX V. 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

25. APPENDIX VI. MINIMUM MADRS TOTAL SCORE CRITERIA AT BASELINE

To be eligible for randomization, Baseline (Visit 2) MADRS total score must be ≥ 22 AND no more than a 25% decrease from the total score at Screening. (Refer to Table below for reference.)

The following formula is to be utilized to determine the MADRS total score change at Baseline (Visit 2):

$$\frac{\text{MADRS total score at Screening - MADRS total score at Baseline}}{\text{MADRS total score at Screening}} \times 100\%$$

MADRS total score at Screening (V1)	MINIMUM Permissible MADRS total score at Baseline (V2)		MADRS total score at Screening (V1)	MINIMUM Permissible MADRS total score at Baseline (V2)
22	22		42	32
23	22		43	33
24	22		44	34
25	22		45	34
26	22		46	35
27	22		47	36
28	22		48	37
29	22		49	37
30	23		50	38
31	24		51	39
32	25		52	40
33	25		53	40
34	26		54	41
35	27		55	42
36	28		56	43
37	28		57	43
38	29		58	44
39	30		59	45
40	31		60	46
41	31		-	-

26. APPENDIX VII. PRE-BASELINE ELIGIBILITY REVIEW

Subject information collected during the Screening Period will be reviewed by the Sponsor Eligibility Committee to inform Inclusion Criterion 19. For each subject who does not screen fail based on any other inclusion or exclusion criterion, sites are instructed to complete the following as soon as possible (within 2 working days, if possible).

- Confirm the diagnosis of bipolar I disorder with at least 1 prior manic episode or manic episode with mixed features corroborated by medical records or documented correspondence with a treating psychiatrist or mental healthcare provider/staff, or information from a reliable informant who is familiar with the subject's psychiatric history.
- Confirm the diagnosis of a current major depressive episode corroborated by medical records or documented correspondence with a treating psychiatrist or mental healthcare provider/staff (if the subject has been evaluated during the current MDD episode), or information from a reliable informant who is familiar with the subject's psychiatric history.
- Send clinical laboratory samples to the centralized laboratory vendor.
- Transmit ECG results to centralized cardiac safety vendor.
- Upload all audio recordings and send all rating scales data to Sponsor's designee. These include:
    - Lifetime Illness Characteristics Questionnaire and Bipolarity Index Score
    - Structured Interview for DSM-5 Clinical Trials (audio recording)
    - Montgomery-Asberg Depression Rating Scale – Self-rating Version
    - Montgomery-Asberg Depression Rating Scale (audio recording)
    - Young Mania Rating Scale
    - Columbia Suicide Severity Rating Scale
    - Clinical Global Impression - Bipolar Version -Severity of Illness
- Complete the following Screening eCRFs or study-level forms:
    - Subject
    - Visit
    - Protocol Version
    - Demographics
    - Medical History
    - Psychiatric History
    - Family Psychiatric and Medical History
    - Prior and Concomitant Medications
    - Vital Signs

- Physical Examination
- Neurological Examination
- Inclusion/Exclusion Criteria
- Screening Pass/Fail

Complete the subject psychiatric narratives based on the subject's self-report, information obtained from medical records, documented correspondence with a treating psychiatrist or mental healthcare provider/staff, or information provided by the highly reliable informant. The narrative should include information summarizing the chronological timeline of subject's psychiatric history including a description of the manic episode and clinical presentation of current major depressive episode.