SEP-4199

Clinical Study Protocol SEP380-201

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SEP-4199 for the Treatment of Major Depressive Episode Associated with Bipolar I Disorder (Bipolar I Depression)

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	Head of Global Clinical Research Psychiatry Sunovion Pharmaceuticals Inc.	Telephone: Email:
Medical Advisor	Associate Medical Director Medical Strategy & Science, Therapeutic Science and Strategy Unit IQVIA	Telephone: US toll-free Intl: Email:
24-Hour Serious Adverse Event/Pregnancy Reporting in the United States	PPD Pharmacovigilance (PVG)	Hotline Number: Email: United States Fax: Outside United States Fax:

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: SEP-4199

Name of Active Ingredient: Non-racemic amisulpride

Proposed Indication: Major Depressive Episode Associated with Bipolar I Disorder (Bipolar I Depression)

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SEP-4199 for the Treatment of Major Depressive Episode Associated with Bipolar I Disorder (Bipolar I Depression)

Study Centers: Approximately 85 sites in the United States (US), Europe, and Japan

Study Objectives

Primary Objective:

- To evaluate the efficacy of SEP-4199 200 mg/day and 400 mg/day compared with placebo for major depressive episode associated with bipolar I depression (diagnosed by DSM-5 criteria) as measured by Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Secondary Efficacy Objective:

- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day compared with placebo on severity of illness as measured by the Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score (depression).

Pharmacokinetic Objectives:

- To evaluate the therapeutic plasma concentration range of SEP-4199 200 mg/day and 400 mg/day for major depressive episode associated with bipolar I disorder.
- To determine the population pharmacokinetics (PK) of SEP-4199 200 mg/day and 400 mg/day.

Other Objectives:

- To determine the relationship between SEP-4199 PK and plasma prolactin for SEP-4199 200 mg/day and 400 mg/day.
- To characterize the exposure-response relationship of SEP-4199 200 mg/day and 400 mg/day and symptoms as measured by MADRS using population pharmacokinetic (PK)/ pharmacodynamics (PD).
- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day compared with placebo on anxiety symptoms, as measured by the Hamilton Rating Scale for Anxiety (HAM-A).
- To evaluate treatment response, defined as ≥ 50% reduction from baseline on the MADRS total score.
- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on symptom remission, defined as a MADRS total score of ≤ 12 after 6 weeks of treatment.
- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on functional impairment associated with bipolar depressive symptoms, as measured by the Sheehan Disability Scale (SDS) total score.

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- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on symptom severity as measured by the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR16) total score.

Safety Objectives:

- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on treatment-emergent mania, as assessed by the YMRS or an AE of mania or hypomania.
- To evaluate safety and tolerability of SEP-4199 200 mg/day and 400 mg/day as measured by physical examinations, 12-lead electrocardiograms (ECG) parameters, vital signs, adverse event (AE) reports, clinical laboratory results, Columbia-Suicide Severity Rating Scale (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Modified Simpson-Angus Scale (SAS).

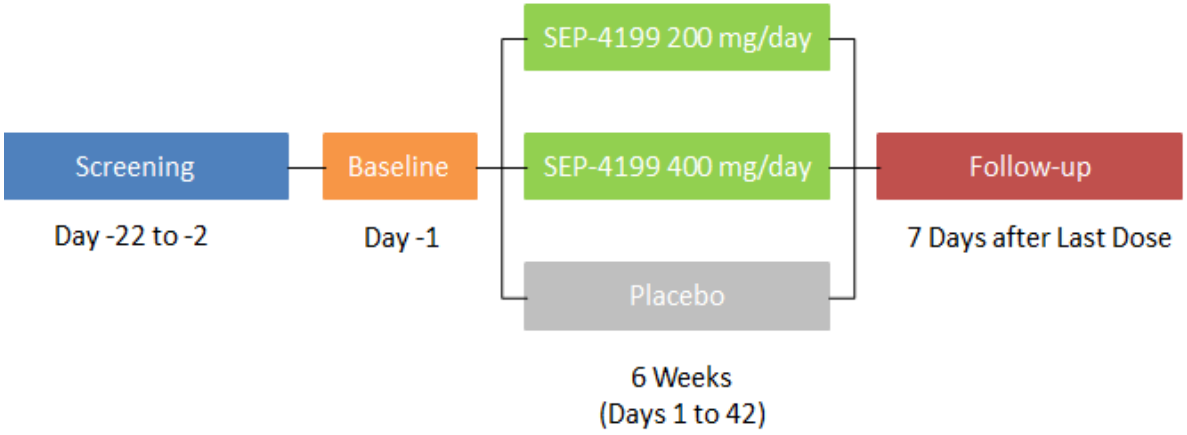
Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study designed to evaluate the efficacy, safety, and tolerability of treatment with SEP-4199 monotherapy given as 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 294 subjects (98 subjects per treatment group) in the US and Europe to one of 3 treatment groups in a 1:1:1 ratio (SEP-4199 200 mg/day or 400 mg/day, or placebo).

In addition, a Japanese cohort will be included in the study to summarize efficacy and safety data for Japanese subjects with bipolar I depression. Approximately 45 subjects (15 subjects per treatment group) will be randomized in the Japanese cohort in a 1:1:1 ratio (SEP-4199 200 mg/day or 400 mg/day, or placebo).

The study will consist of Screening (up to 21 days), 6 weeks of treatment (42 days), and follow-up (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.

Study Schematic – All Subjects



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Screening Period (Day -22 to -2) Informed consent will be obtained from each subject before any study procedures are performed for this study. Study eligibility criteria will be assessed during this period, and subjects will be washed out from prior or concomitant medications, where applicable, prior to randomization. Psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) are to be discontinued as tolerated and clinically appropriate at least 3 days prior to randomization. Per local clinical practice, subjects may be hospitalized for up to 7 days during the Screening period. Further need for hospitalization during the Screening period will require consultation with the Medical Monitor. Baseline (Day -1) and Treatment Period (Day 1 through Day 42) Subjects who meet eligibility criteria at Screening will return to the study site on Day -1 for confirmation of screening evaluations as well as completion of predose assessments. Eligible subjects (based on confirmation of study entry criteria) will be randomized and dispensed study drug at Day -1. Per local clinical practice, subjects may be hospitalized for up to 7 days during the first week of treatment with double-blind study drug. Further need for hospitalization will require consultation with the Medical Monitor. Subjects will self-administer the study drug on an outpatient basis once daily with or without food beginning on Day 1 (the day after the Baseline visit) and continue for 6 weeks (the last dose of study drug will be self-administered by the subject at home on the morning of Visit 6). Subjects will be instructed to administer study drug as a single oral dose in the morning at approximately the same time each day. Clinic visits are to begin no later than 6 hours postdose, if possible. During the baseline (Day -1) and treatment period (Days 1 to 42), subjects will have clinic visits at Days -1, 7, 14, and 28. In order to facilitate scheduling of clinic visits, a window of ± 2 days will be allowed for each clinic visit. Subjects will have a telephone contact at Day 35 (± 2). End of Treatment (EOT)/Early Termination (ET) (Day 42 [± 2]) Subjects will have a clinic visit at Day 42 for assessments of efficacy and safety. Subjects who discontinue the study prior to this visit will undergo the procedures and assessments for this visit at the time of discontinuation. Follow-up Period (Day 49 [± 2]) All subjects who received at least one dose of study drug will have a follow-up visit for safety and tolerability assessments 7 (± 2) days after their last study drug dose. Assessment of potential withdrawal effects will also be made during the follow-up period. Efficacy, Safety, and PK/PD Assessments Efficacy will be evaluated using the MADRS, CGI-BP-S, and HAM-A. Treatment response and symptom remission will be assessed using the MADRS. Additional assessments will include evaluation of functional impairment associated with bipolar depressive symptoms using the SDS total score and symptom severity using the QIDS-SR16 total score. Safety and tolerability will be monitored throughout the study by physical examinations, ECGs, vital signs, adverse event monitoring, clinical laboratory tests, YMRS, and C-SSRS. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation. Assessment of potential withdrawal effects will be conducted via administration of the Physician's Withdrawal Checklist. Movement disorders will be assessed by AIMS, BARS, and Modified SAS. A Data and Safety Monitoring Board

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(DSMB) will review safety data at regular intervals during the study.

Blood samples will be collected for population pharmacokinetics. Blood samples will be analyzed for plasma concentrations of R- and S-amisulpride and plasma prolactin. 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 CRF (Visits 4 and 6 only). Plasma samples collected for PK concentration 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.

Number of Subjects (planned) US and Europe

Approximately 294 subjects (N = 98 per treatment group) will be randomized in the US and Europe.

Number of Subjects (planned) Japanese Cohort

Approximately 45 subjects (N = 15 per treatment group) will be randomized in Japan.

Main Diagnosis and Criteria for Enrollment

Primary Inclusion Criteria (not all inclusive):

- Subject provides written informed consent to participate in the study.
- Subject is 18 to 65 years of age, inclusive, at the time of informed consent with 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 (diagnosed by DSM-5 criteria, and confirmed by the Structured Clinical Interview for DSM-5-Clinical Trial Version [SCID-5-CT]). The current episode of major depression associated with bipolar I disorder must be confirmed by the investigator and noted in the source records.
- Subject must have a lifetime history of at least one bipolar manic or mixed manic episode. It is strongly recommended that a reliable informant (eg, family member or caregiver) be available to confirm this history.
- Subject's current major depressive episode is ≥ 4 weeks and less than 12 months in duration.
- Subject has a MADRS total score ≥ 22 at both Screening and Baseline.
- Subject has a YMRS total score ≤ 12 at Screening.

Primary Exclusion Criteria (not all inclusive):

- Subject has a lifelong history or presence of symptoms consistent with a major psychiatric disorder other than bipolar I disorder as defined by DSM-5. Exclusionary disorders include but are not limited to moderate to severe alcohol use disorder (within past 12 months), substance use disorder (other than nicotine or caffeine) within past 12 months, bipolar II disorder, schizoaffective disorder, obsessive compulsive disorder, posttraumatic stress disorder.
- Subject demonstrates a decrease (improvement) of ≥ 25% in MADRS total score from Screening to Baseline, or subject's MADRS total score is < 22 at Baseline.
- Subject has a history of non-response to an adequate (6-week) trial of three or more antidepressants (with or without mood stabilizers) during the current episode.

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• Subject is considered by the Investigator to be at imminent risk of suicide or injury to self, others, 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 90 days]) or Baseline. The complete listing of study entry criteria is provided in Section 8.
Investigational Product, Dosage and Mode of Administration SEP-4199 will be supplied as 100 mg tablets and 200 mg tablets each containing a fixed ratio of 85:15 (R-amisulpride:S-amisulpride). Two 100 mg tablets will be given for the 200 mg dose and two 200 mg tablets will be given for the 400 mg dose. 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 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 randomization. Subjects treated with fluoxetine or olanzapine plus fluoxetine combination must discontinue these medications at least 28 days prior to randomization. Depot neuroleptics must have been discontinued at least one treatment cycle prior to randomization. Subjects treated with MAO inhibitors must discontinue these medications at least 21 days prior to randomization. Treatment with sedative hypnotics (for insomnia) is permitted during the screening period, but should be tapered as clinically appropriate to conform with and adequately prepare the subject for the protocol-specified dosing limitations applicable to these agents following randomization. The use of herbal supplements or other complementary or alternative medications during the trial is not permitted. Further details are provided in Section 10.3.
Criteria for Evaluation **Primary Efficacy Endpoint:** • Change from baseline in MADRS total score at Week 6.

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Secondary Efficacy Endpoint:

- Change from baseline in global severity assessed by the CGI-BP-S score (depression) at Week 6.

Pharmacokinetic Endpoints:

- Plasma concentrations of R- and S-amisulpride.
- Plasma concentrations of prolactin.

Other Endpoints:

- Number and percentage of treatment responders, defined as ≥ 50% reduction from baseline in MADRS total score at Week 6.
- Time to treatment response, defined as ≥ 50% reduction from baseline MADRS total score.
- Change from baseline in anxiety symptoms based on the HAM-A total score at Week 6.
- Incidence of symptom remission, defined as a MADRS total score of ≤ 12 at Week 6.
- Time to remission, defined as MADRS total score of ≤ 12.
- Functional impairment assessed by change from baseline in the SDS total score at Week 6.
- Subject self-report of overall depressive symptom severity, assessed by change from baseline in the QIDS-SR16 total score at Week 6.

Safety Endpoints:

- Incidence of treatment-emergent mania, defined as a YMRS score of ≥ 16 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania.
- Incidence of adverse events (AEs), discontinuation due to AEs, and serious AEs (SAEs).
- Changes in weight, clinical laboratory tests, vital signs, and ECG measurements.
- Change from baseline in AIMS, BARS, and Modified SAS.
- Frequency and severity of suicidal ideation and suicidal behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Japanese Cohort Endpoints:

- All efficacy, pharmacokinetic, pharmacodynamic, and safety endpoints will be evaluated and summarized for the Japanese cohort.

Statistical Methods

General Methodology

The primary efficacy analysis will be based on the intention-to-treat (ITT) population, which includes all subjects who are randomized. The safety population includes all subjects who are randomized and receive at least 1 dose of study medication. In general, all analyses of the Japanese cohort are descriptive in nature and will be reported separately unless otherwise specified.

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Primary Efficacy Analysis: The primary efficacy estimand is defined as the efficacy of each SEP-4199 dose over placebo for 6 weeks calculated as the difference in the primary efficacy endpoint (change from baseline in the MADRS total score at Week 6) between each SEP-4199 treatment group and the placebo treatment group in the ITT population. This estimand, which will only include those subjects who participated in sites located in the US and Europe provides an estimate of the efficacy of each SEP-4199 dose over placebo, should a subject be able to tolerate and adhere to treatment for 6 weeks. The analysis method makes a missing at random (MAR) assumption to the missing primary efficacy endpoints. A mixed model for repeated measures (MMRM) that includes terms for treatment, visit, region, baseline MADRS total score, and the treatment-by-visit interaction will be used for the primary efficacy analysis. An unstructured covariance matrix will be used for the within-subject correlation. The comparisons of SEP-4199 200 mg/day and SEP-4199 400 mg/day versus placebo at Week 6 will be adjusted for multiplicity using the truncated Hochberg (γ) procedure with truncation parameter, $\gamma = 0.9$ (Dmitrenko 2017). To evaluate the robustness of the MMRM results for the primary efficacy endpoint with respect to the MAR assumption, sensitivity analyses based on a Missing Not At Random (MNAR) assumption will be performed. A supplementary analysis of the primary efficacy of SEP-4199 will be conducted to explore the dose response relationship using the Multiple Comparison Procedure – Modelling (MCP-Mod) methodology. Possible dose response shapes to assess include linear, quadratic, Emax, and sigmoidal Emax. The best model fit will be selected using the minimum Akaike information criterion out of the statistically significant multiple contrast tests based on optimal contrast coefficients. Once the best model is selected, target dose(s) of interest including the minimum effective dose (MED) will be explored. Secondary Efficacy Analyses: The CGI-BP-S score (depression) will be analyzed by the MMRM method described for the primary efficacy endpoint using the ITT population with the appropriate baseline used as the covariate. The CGI-BP-S secondary endpoint at Week 6 along with the primary endpoint at Week 6 will be tested using a mixture-based gatekeeping procedure to control the global familywise error rate (FWER). This gatekeeping procedure is constructed using two component procedures. Once the primary objective of at least one primary endpoint is met using a truncated Hochberg ($\gamma = 0.9$), the second component, the CGI-BP-S hypotheses, will be tested using a regular Hochberg procedure. A hypothesis is testable in a latter family only if the hypothesis in the former family associated with the same dose level is rejected. Other Efficacy Analyses: The HAM-A and the QIDS-SR16 total score will be analyzed by the MMRM method described for the primary efficacy endpoint using the ITT population with the appropriate baseline used as the covariate. The SDS and EuroQoL 5 dimensional questionnaire (EQ-5D-5L) total scores will be analyzed using an ANCOVA model with treatment, region as fixed effects, and appropriate baseline as a covariate. The MADRS total score responder proportions at Week 6 will be compared among the 3 treatment arms using logistic regression. This model will include treatment and region as fixed effects and baseline MADRS score as a covariate. The log rank testing method will be used to test for differences among the treatments for time to MADRS responder response. The analysis will be supplemented with Kaplan-Meier curves to illustrate the differences among the three treatments.

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A cumulative distribution curve of treatment response for each treatment group will be presented.

Remission incidence rates will be analyzed similarly to the MADRS responder analysis.

The R- and S-amisulpride and plasma prolactin concentrations will be listed and summarized descriptively by dose level.

The complete methodology and results of the population pharmacokinetic and pharmacodynamic analyses will be reported separately.

Safety Analyses:

AEs (or SAEs) and AEs leading to discontinuation will be summarized by number and percentage of subjects for each treatment group by system organ class and preferred term. AEs will also be reported by maximum severity and by relationship to study drug.

Mania incidence rates (YMRS) will be analyzed similarly to the MADRS responder analysis (as described above).

Descriptive statistics will be provided by treatment for observed values or changes from baseline for weight, laboratory parameters, vital signs, and ECG parameters. The incidence of subjects with elevated QTcF intervals: (> 450 for males and > 470 for females) and (> 500 msec for males or females) and changes in QTc intervals ≥ 30 msec, but < 60 msec and ≥ 60 msec will be summarized by treatment group.

Rank ANCOVA with adjustments for baseline value will be applied to change from baseline in serum prolactin, lipids, glucose, weight, and body mass index (BMI) for comparison between each SEP-4199 group and placebo.

Movement disorder measures (AIMS, BARS, and Modified SAS) will be analyzed using MMRM based on the change from baseline to Week 6.

The frequency and severity of suicidal ideation or suicidal behavior in the C-SSRS will be provided for each time point as appropriate.

Japanese Cohort Analyses:

In general, descriptive statistics will be used to summarize the efficacy and safety of the Japanese cohort. An additional exploratory analysis with the Japanese cohort primary efficacy data will be performed by replacing region (US, EU) with region (US, EU, Japan) in the MMRM primary model. The Japanese cohort alone will also be analyzed using an MMRM method.

In general, safety analyses will be repeated for the Japanese Cohort using descriptive statistics.

Sample Size:

A total sample size of 279 evaluable subjects in US and Europe (93 per treatment group: SEP-4199 200 mg/day, SEP-4199 400 mg/day, and placebo) with a 2-sided global alpha of 0.05 will provide about 90% power to reject at least 1 truly significant comparison and about 75% power to reject both truly significant comparisons using the truncated Hochberg ($\gamma = 0.9$) procedure, assuming treatment effect sizes of 0.44 for both doses of SEP-4199. The effect sizes were selected considering the data from the completed lurasidone bipolar depression study (Loebel 2014). This effect size corresponds to a treatment difference of -3.85 for a SEP-4199 dose with a common standard deviation of 8.745 on the MADRS scale change from baseline at Week 6. An upward adjustment of approximately 5% is used to compensate for information lost due to subjects who are randomized and do not provide any postbaseline primary efficacy data. The total sample size will be approximately 294 randomized subjects (or N = 98 subjects per treatment group).

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The sample size was calculated using the Mediana package version 1.05 within R version 3.4.2 (R Core Team 2017). The sample size for the Japanese Cohort (45 total [N = 15 subjects per group], including 9 dropouts) provides more than 80% probability to have a treatment difference point estimate greater than zero for the MADRS.

Table 2: Schedule of Assessments

	Screen	Baseline and Treatment					EOT/ET	Follow-up
Study Visit Number	**Visit 1[a]**	**Visit 2[a,b]**	**Visit 3**	**Visit 4**	**Visit 5**	**TC**	**Visit 6[c]**	**Visit 7**
Study Visit Day	**-22 to -2**	**-1**	**7±2**	**14±2**	**28±2**	**35±2**	**42±2**	**49±2**
Study Procedures								
Informed consent	X							
Inclusion/Exclusion Criteria Review	X	X						
Randomization		X						
Dispense Study Drug		X	X	X	X			
Study Drug Accountability[d]			X	X	X		X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X
Pretreatment Event Monitoring	X	X						
Adverse Event Monitoring			X	X	X	X	X	X
Schedule Next Visit[e]	X	X	X	X	X	X	X	
Demographics	X							
Medical History	X							
Psychiatric History/Mental Status[f]	X							
Structured Clinical Interview for DSM-Clinical Trial Version (SCID-5-CT)[g]	X							
Physical Examination	X	X					X	X
Neurological Examination	X	X					X	
Height	X							
Weight (Including Body Mass Index)[h]	X	X					X	X
Waist Circumference		X					X	X
Vital Signs[i]	X	X	X	X	X		X	X
12-Lead Electrocardiogram (ECG)	X	X	X	X	X		X	X
Montgomery-Asberg Depression Rating Scale (MADRS)[j]	X	X	X	X	X		X	
Hamilton Rating Scale for Anxiety (HAM-A)		X	X	X	X		X	
Young Mania Rating Scale (YMRS)[k]	X	X	X	X	X		X	X
Sheehan Disability Scale (SDS)		X					X	
Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR16)		X	X	X	X		X	
Abnormal Involuntary Movement Scale (AIMS)		X	X	X	X		X	
Barnes Akathisia Rating Scale (BARS)		X	X	X	X		X	
Modified Simpson-Angus Scale (SAS)		X	X	X	X		X	

Table 2: Schedule of Assessments (Continued)

	Screen	Baseline and Treatment					EOT/ET	Follow-up
Study Visit Number	**Visit 1[a]**	**Visit 2[a,b]**	**Visit 3**	**Visit 4**	**Visit 5**	**TC**	**Visit 6[c]**	**Visit 7**
Study Visit Day	**-22 to -2**	**-1**	**7±2**	**14±2**	**28±2**	**35±2**	**42±2**	**49±2**
Columbia-Suicide Severity Rating Scale (C-SSRS)[l]	X	X	X	X	X		X	X
Physician Withdrawal Checklist							X	X
Clinical Global Impression – Bipolar Version-Severity of Illness (CGI-BP-S)		X	X	X	X		X	
EuroQoL-5D (EQ-5D-5L)		X					X	
Hepatitis B/C	X							
Urine Drug Screen	X	X		X			X	X
Serum Thyroid Stimulating Hormone	X							
Serum Follicle Stimulating Hormone (Female Subjects)	X							
Serum β-hCG (Female Subjects of childbearing potential)[m]	X							
Urine β-hCG (Female Subjects of childbearing potential)[m]		X		X			X	X
Hematology, Serum Chemistry, and Urinalysis[n]	X	X		X			X	X
Serum Prolactin[o,p]	X	X		X			X	X
Hemoglobin A1c (HbA1c)	X	X					X	
Lipid Panel[n]	X	X					X	
Serum Insulin	X	X					X	
High-sensitivity (hs) CRP	X	X					X	
Blood Sample for R- and S-Amisulpride PK and Plasma prolactin[p]	X	X		X			X	X

Abbreviations: BMI = body mass index; CRF = case report form; CRP = C-reactive protein; 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 Contact.

[a] Per local clinical practice, subjects may be hospitalized for up to 7 days during the Screening period and/or during the first week of treatment with double-blind investigational product. Further need for hospitalization will require consultation with the Medical Monitor.

[b] 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).

[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. All subjects who complete the treatment period and those who discontinue early will complete a follow-up visit 7 (±2) days after the last dose of study drug.

[d] Clinical site staff will record the date and time of the 3 doses prior to the study visit in the source (all visits) and CRF (Visits 4 and 6 only), based on subject self-report.

Footnotes continue on next page.

[e] Instruct subject to record dosing date and time of the last 3 doses prior to the study visit on the blisterpack wallet and bring back all used/unused study drug and packaging to next visit.
[f] 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.
[g] The SCID-5-CT will be used to support the DSM-5 diagnosis and must be administered by a qualified rater at the site.
[h] BMI will be calculated by clinical site staff at Screening and recorded in the CRF. At visits 2, 6, and 7, BMI does not need to be calculated by the clinical site staff as it will be calculated in the analysis.
[i] Vital signs measurements will include orthostatic changes in blood pressure and heart rate. After being in a supine position for ≥ 5 minutes, systolic and diastolic blood pressures, respiratory rate, pulse rate, and temperature will be collected. 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.
[j] To be eligible for enrollment, subjects must have a MADRS total score ≥ 22 at Screening. Subjects who demonstrate 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 24, Appendix V).
[k] To be eligible for enrollment, subjects must have a YMRS total score ≤ 12 at Screening.
[l] 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.
[m] Any positive urine β-human chorionic gonadotropin (hCG) test should be confirmed by serum β-hCG.
[n] Subjects are to fast overnight for at least 8 hours (no food after midnight) prior to blood sample collection for laboratory testing at Visits 2 and 6; it is also recommended for Visit 1 so as to avoid potential retests.
[o] Prolactin levels (serum and plasma) will be blinded except for results from Visit 1 (Screening).
[p] Blood sample for SEP-4199 population pharmacokinetic analysis for R- and S-enantiomers and/or plasma prolactin measurement will be collected at Visits 1, 2, 4, 6 and 7, with a record of the time of last 3 doses on the CRF at Visits 4 and 6. The blood sample will be collected at time of clinical safety laboratory test sample collection. Plasma concentrations of R- and S-amisulpride and plasma prolactin levels will be measured. Remaining plasma from samples 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.

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

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CFR	Code of Federal Regulations
CGI-BP-S	Clinical Global Impression – Bipolar Version-Severity of Illness
CRF	Case report form (or electronic case report form)
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DBL	Database lock
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
EPS	Extrapyramidal symptoms
EQ-5D-5L	EuroQoL 5 dimensional questionnaire
ET	Early termination
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HAM-A	Hamilton Rating Scale for Anxiety

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
hs	High sensitivity
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
IUD	Intrauterine device
IXRS	Interactive Voice/Web-based Response System
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MAO	Monoamine oxidase
OTC	Over-the-counter
PCS	Potentially clinically significant
PK	Pharmacokinetic(s)
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
PVG	Pharmacovigilance
QIDS	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
RO_{50}	Dose (mg) for 50% occupancy
RR	RR interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SCID-CT	Structured Clinical Interview for DSM-Clinical Trial Version
SDS	Sheehan Disability Scale
SOC	System organ class

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
SOP	Standard Operating Procedure
TdP	Torsades de pointes
US	United States
WHO-DD	World Health Organization drug dictionary
YMRS	Young Mania Rating Scale

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
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 enrolled/randomized.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and/or active control.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and was assigned a randomization number.
Enrolled Subject	Any subject who was successfully screened and enrolled into the pre-randomization period of the study.
Randomization Failures	Any subject who was enrolled but not randomized.
Completed Subject	Any subject who 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.
End of Study	The day of the last visit by the last subject in the study.

4. INTRODUCTION

4.1. Background

Bipolar spectrum illness (BD I, BD II, BD NOS) is estimated to affect 4.4% of the US population (Merikangas 2007). Bipolar disorder causes more marked functional impairment (Shippee 2011) and has a greater impact on quality of life than unipolar depression (Gutierrez-Rojas 2008). Bipolar patients 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 and heterogeneity of clinical presentations, which may involve mixed symptoms with depression predominating. Although the pharmacologic treatment of bipolar depression continues to be dominated by three major classes of drugs, the anticonvulsants, atypical antipsychotics, and serotonergic antidepressants, these treatments have significant limitations including tolerability and undesirable side effects such as metabolic derangement, weight gain, sedation/somnolence, sexual dysfunction, extrapyramidal symptoms and akathisia (Kemp 2014). In addition, treatment of bipolar depression with antidepressants remains controversial due to concerns about switching patients into hypomania, mania, or more rapid cycling (APA 2002).

Amisulpride is approved in Italy, Czech Republic, and Portugal for the treatment of dysthymia at a low dose of 50 mg/d (Lecrubier 1997). In vitro radioligand binding studies show that racemic amisulpride has high affinity for serotonin 5-HT7 receptors in addition to dopamine D2 receptors (Abbas 2009). Preclinical pharmacology studies using 5-HT7 knockout mice suggest that the antidepressant-like effects of amisulpride are mediated via 5-HT7 receptor antagonism (Abbas 2009).

Sunovion is developing SEP-4199 for the treatment of major depressive episode associated with bipolar I disorder.

4.2. Study Conduct Rationale

The current study is designed to evaluate SEP-4199 for the treatment of major depressive episode associated with bipolar I disorder.

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 D2 receptor occupancy. To improve the benefit/risk profile of amisulpride in mood disorders, SEP-4199 has been designed with a non-racemic ratio of enantiomers (85% R-amisulpride: 15% S-amisulpride) designed to optimally target ≤ 50% D2 occupancy. In this way, SEP-4199 maximizes the 5-HT7 antagonist activity of amisulpride while reducing the level of D2 antagonism to the minimum associated with antidepressant benefit, in order to limit D2-associated undesirable side effects. This pharmacologic profile is expected to confer

significant antidepressant benefits in those patients with more severe forms of depression, such as depressive episodes associated with bipolar disorder, and in patients with disorders characterized by mixed mood/psychotic symptoms.

5. STUDY OBJECTIVES

5.1. Primary Objective

- To evaluate the efficacy of SEP-4199 200 mg/day and 400 mg/day compared with placebo for major depressive episode associated with bipolar I disorder (diagnosed by DSM-5 criteria) as measured by Montgomery-Asberg Depression Rating Scale (MADRS) total score.

5.2. Secondary Efficacy Objective

- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day compared with placebo on severity of illness as measured by the Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S) score (depression).

5.3. Pharmacokinetic Objectives

- To evaluate the therapeutic plasma concentration range of SEP-4199 200 mg/day and 400 mg/day for major depressive episode associated with bipolar I disorder.
- To determine the population pharmacokinetics (PK) of SEP-4199 200 mg/day and 400 mg/day.

5.4. Other Objectives

- To determine the relationship between SEP-4199 PK and plasma prolactin for SEP-4199 200 mg/day and 400 mg/day.
- To characterize the exposure-response relationship of SEP-4199 200 mg/day and 400 mg/day and symptoms as measured by MADRS using population pharmacokinetic (PK)/pharmacodynamics (PD).
- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day compared with placebo on anxiety symptoms, as measured by the Hamilton Rating Scale for Anxiety (HAM-A).
- To evaluate treatment response, defined as ≥ 50% reduction from baseline on the MADRS total score.
- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on symptom remission, defined as a MADRS total score of ≤ 12 after 6 weeks of treatment.
- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on functional impairment associated with bipolar depressive symptoms, as measured by the Sheehan Disability Scale (SDS) total score.

- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on symptom severity as measured by the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16) total score.

5.5. Safety Objectives

- To evaluate the effect of SEP-4199 200 mg/day and 400 mg/day on treatment-emergent mania, as assessed by the YMRS or an AE of mania or hypomania.
- To evaluate safety and tolerability of SEP-4199 200 mg/day and 400 mg/day as measured by physical examinations, 12-lead electrocardiograms (ECG) parameters, vital signs, adverse event (AE) reports, clinical laboratory results, Columbia-Suicide Severity Rating Scale (C-SSRS), Abnormal Involuntary Movement Scale (AIMS) Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS).

6. STUDY ENDPOINTS

6.1. Primary Efficacy Endpoint

- Change from baseline in MADRS total score at Week 6.

6.2. Secondary Efficacy Endpoint

- Change from baseline in global severity assessed by the CGI-BP-S score (depression) at Week 6.

6.3. Pharmacokinetic Endpoints

- Plasma concentrations of R- and S-amisulpride.
- Plasma concentrations of prolactin.

6.4. Other Endpoints

- Number and percentage of treatment responders, defined as ≥ 50% reduction from baseline in MADRS total score at Week 6.
- Time to treatment response, defined as ≥ 50% reduction from baseline MADRS total score.
- Change from baseline in anxiety symptoms based on the HAM-A total score at Week 6.
- Incidence of symptom remission, defined as a MADRS total score of ≤ 12 at Week 6.
- Time to remission, defined as MADRS total score of ≤ 12.
- Functional impairment assessed by change from baseline in the SDS total score at Week 6.

- Subject self-report of overall depressive symptom severity, assessed by change from baseline in the QIDS-SR16 total score at Week 6.

6.5. Safety Endpoints

- Incidence of treatment-emergent mania, defined as a YMRS score of ≥ 16 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania.
- Incidence of adverse events (AEs), discontinuation due to AEs, and serious AEs (SAEs).
- Changes in weight, clinical laboratory tests, vital signs, and ECG parameters.
- Change from baseline in AIMS, BARS, and SAS.
- Frequency and severity of suicidal ideation and suicidal behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS).

6.6. Japanese Cohort Endpoints

- All efficacy, pharmacokinetic, pharmacodynamic, and safety endpoints will be evaluated and summarized for the Japanese cohort.

7. INVESTIGATIONAL PLAN

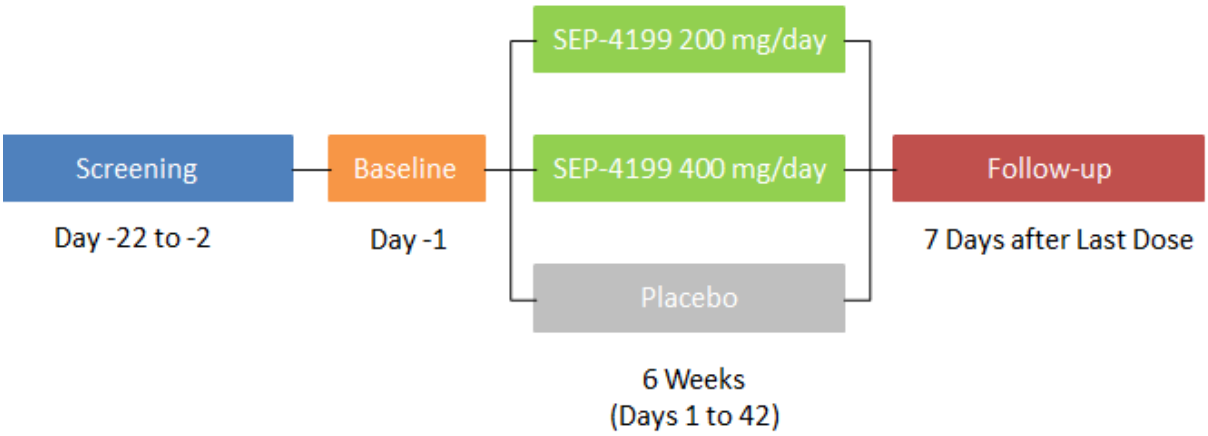
7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study designed to evaluate the efficacy, safety, and tolerability of treatment with SEP-4199 monotherapy given as 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 294 subjects (98 subjects per treatment group) in the US and Europe to one of 3 treatment groups in a 1:1:1 ratio (SEP-4199 200 mg/day or 400 mg/day, or placebo).

In addition, a Japanese cohort will be included in the study to summarize efficacy and safety data for Japanese subjects with bipolar I depression. Approximately 45 subjects (15 subjects per treatment group) will be randomized in the Japanese cohort in a 1:1:1 ratio (SEP-4199 200 mg/day or 400 mg/day, or placebo).

The study will consist of Screening (up to 21 days), 6 weeks of treatment (42 days), and follow-up (7 [±2] days after the last study drug dose). A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2, Schedule of Assessments, and Section 11, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic – All Subjects



Screening Period (Day -22 to -2)

Informed consent will be obtained from each subject before any study procedures are performed for this study. Study eligibility criteria will be assessed during this period, and subjects will be washed out from prior or concomitant medications, where applicable, prior to randomization. Psychotropic medications (eg, antipsychotic agents, antidepressants, and mood stabilizers) are to be discontinued as tolerated and clinically appropriate at least 3 days prior to randomization.

Per local clinical practice, subjects may be hospitalized for up to 7 days during the Screening period. Further need for hospitalization during the Screening period will require consultation with the Medical Monitor.

Baseline (Day -1) and Treatment Period (Day 1 through Day 42)

Subjects who meet eligibility criteria at Screening will return to the study site on Day -1 for confirmation of screening evaluations as well as completion of predose assessments. Eligible subjects (based on confirmation of study entry criteria) will be randomized and dispensed study drug at Day -1.

Per local clinical practice, subjects may be hospitalized for up to 7 days during the first week of treatment with double-blind study drug. Further need for hospitalization will require consultation with the Medical Monitor.

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

During the baseline (Day -1) and treatment period (Days 1 to 42), subjects will have clinic visits at Days -1, 7, 14, and 28. In order to facilitate scheduling of clinic visits, a window of ± 2 days will be allowed for each clinic visit. Subjects will have a telephone contact at Day 35 (± 2).

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

Subjects will have a clinic visit at Day 42 for assessments of efficacy and safety. Subjects who discontinue the study prior to this visit will undergo the procedures and assessments for this visit at the time of discontinuation.

Follow-up Period (Day 49 [± 2])

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

Efficacy, Safety, and PK/PD Assessments

Efficacy will be evaluated using the MADRS, CGI-BP-S, and HAM-A. Treatment response and symptom remission will be assessed using the MADRS. Additional assessments will include evaluation of functional impairment associated with bipolar depressive symptoms using the SDS total score and symptom severity using the QIDS-SR16 total score.

Safety and tolerability will be monitored throughout the study by physical examinations, ECGs, vital signs, adverse event monitoring, clinical laboratory tests, YMRS, and C-SSRS. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation. Assessment of potential withdrawal effects will be conducted via administration of the Physician's Withdrawal Checklist. Movement disorders will be assessed by AIMS, BARS, and SAS.

A Data and Safety Monitoring Board (DSMB) will review safety data at regular intervals during the study.

Blood samples will be collected for population pharmacokinetics. Blood samples will be analyzed for plasma concentrations of R- and S-amisulpride and plasma prolactin. 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 CRF (Visits 4 and 6 only). Plasma samples collected for PK concentration 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.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

After a subject provides consent, a unique subject number will be assigned at screening, consisting of a 3-digit protocol number, 3-digit site number, and a unique 3-digit subject identifier (eg, the second screened subject from site #005 will be 201005002). Subjects will be numbered consecutively. No subject numbers are to be reused once assigned. This number will track a subject throughout their participation in the study.

Subjects who passed study entry criteria and did not get randomized can be rescreened once to determine eligibility. Subjects who are rescreened must be assigned a new screening number.

Randomization will be stratified by region. The treatment schedule will be generated by a non-study biostatistician. Once a subject is deemed eligible to be randomized at Day -1, an interactive voice/web-based system (IXRS) will perform the treatment assignment. Subjects will be randomized to 1 of 3 treatments in a 1:1:1 ratio:

- SEP-4199 200 mg/day
- SEP-4199 400 mg/day
- Placebo QD

7.2.2. Blinding

Subjects, Investigators, clinical site staff, persons performing the assessments, clinical operations personnel (including the sponsor's bioanalytical manager), data analysts, and personnel at central laboratories (including imaging) will remain blinded to the identity of the treatment from the time of randomization until unblinding, using the following methods:

- 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, 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 blinded except for results from Visit 1 (Screening).

- 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.
- Study results, including unblinded data and randomization files, obtained in the US and Europe will not be published or disseminated to the Japan sites, Japan investigators or other personnel directly involved in the conduct of the study prior to the completion of the Japanese cohort. After unblinding of the US and Europe cohort, any personnel directly involved in the conduct of the US and Europe cohort will not be directly involved in the conduct of the Japanese cohort.

Plasma concentrations of R-amisulpride, S-amisulpride, and total amisulpride will not be disclosed before unblinding of each cohort, respectively. 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 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. 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 11.6.4. 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 Dosages

The enantiomers of amisulpride are stereoselective for 2 distinct therapeutic targets. The S-enantiomer is stereoselective for antagonism of dopamine D2 receptors. The R-enantiomer is stereoselective for antagonism of serotonin 5-HT7 receptors.

In PET imaging of healthy volunteers, D2 occupancies below 50% are achieved following single doses of the S-enantiomer below 100 mg. In polysomnography of healthy volunteers, serotonergic effects (REM suppression) are achieved following single doses of the R-enantiomer at 340 mg and 600 mg.

The ratio of 85:15 R:S-amisulpride (SEP-4199) is optimal for maximizing doses for serotonergic 5-HT7 antagonism in a dose range which does not exceed 50% dopamine D2 occupancy. In PET imaging of healthy volunteers, D2 occupancies of 20-30% and 40-50% are achieved following single doses of 200 mg and 400 mg SEP-4199 (85:15), respectively. Thus, these fixed doses of SEP-4199 as a non-racemic 85:15 ratio will be utilized in this study.

7.3.2. 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.

7.3.3. Rationale for the Endpoints

The efficacy assessments and their timing are considered appropriate to assess the efficacy of SEP-4199 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 15.3.9 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Subject is 18 to 65 years of age, inclusive, at the time of informed consent with 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 (diagnosed by DSM-5 criteria, and confirmed by the SCID-5-CT). The current episode of major depression associated with bipolar I disorder must be confirmed by the Investigator and noted in the source records.
2. Subject provides written informed consent and is willing and able to comply with the protocol in the opinion of the investigator.
3. 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.
4. Subject must have a lifetime history of at least one bipolar manic or mixed manic episode. It is strongly recommended that a reliable informant (eg, family member or caregiver) be available to confirm this history.
5. Subject's current major depressive episode is ≥ 4 weeks and less than 12 months in duration at Screening.
6. Subject has a MADRS total score ≥ 22 at both Screening and Baseline.
7. Subject has a YMRS total score ≤ 12 at Screening.
8. Female subjects of childbearing potential must have a negative serum ß-hCG test at Screening.
9. Females who participate in this study must be one of the following:
   - Unable to become pregnant (eg, postmenopausal, surgically sterile, etc.)
   - Practicing abstinence or part of an abstinent lifestyle
   - Using and will continue to use a highly effective form of birth control for at least 28 days prior to administration of the first dose of study drug, during the treatment period, and 2 months after completion or premature discontinuation from the study drug. See Section 10.4 for further information on acceptable methods of birth control.
10. Male subjects with partners of child bearing potential must be practicing abstinence, part of an abstinent lifestyle or using protocol-specified methods of birth control. See Section 10.4 for further information on acceptable methods of birth control.
11. Subject is in good physical health on the basis of medical history, physical examination, and laboratory screening.

12. Subjects with type 2 diabetes are eligible for study inclusion only if all of the following conditions are met within 30 days prior to Screening:
    - Subject's random screening glucose is < 200 mg/dL (11.1 mmol/L).
    - Subject's Hemoglobin A1c (HbA1c) ≤ 7.0%.
    - If a subject is currently being treated with oral anti-diabetic medication(s), the dose must have been stable for at least 30 days prior to screening. Such medication may be adjusted or discontinued during the study, as clinically indicated.
    - Subject has not required hospitalization for diabetes or related complications in the past 12 months.
    - Note: Subjects with type 2 diabetes that is newly diagnosed during screening are ineligible for the study.
13. Subject who requires concomitant medication treatment with the following agents may be included if they have been on stable doses for the specified times: 1) oral hypoglycemics must be stabilized for at least 30 days prior to baseline; 2) thyroid hormone replacement must be stable for at least 90 days prior to baseline; 3) anti-hypertensive agents must be stable for at least 30 days prior to baseline. The subject's medical condition should be deemed clinically stable following consultation with the Medical Monitor as needed.

8.2. Subject Exclusion Criteria

The subjects who meet any of the following criteria will be excluded in the study.

1. Subject has a lifelong history or presence of symptoms consistent with a major psychiatric disorder other than bipolar I disorder as defined by DSM-5. Exclusionary disorders include but are not limited to moderate to severe alcohol use disorder (within past 12 months), substance use disorder (other than nicotine or caffeine) within past 12 months, bipolar II disorder, schizoaffective disorder, obsessive compulsive disorder, posttraumatic stress disorder.
2. Subject demonstrates a decrease (improvement) of ≥ 25% in MADRS total score from Screening to Baseline, or subject's MADRS total score is < 22 at Baseline.
3. Subject has received treatment with antidepressants within 3 days of randomization, fluoxetine at any time within 28 days, an MAO inhibitor within 21 days or clozapine within 120 days. All other psychotropic medications with the exceptions of lorazepam, temazepam, eszopiclone, zopiclone, zolpidem and zolpidem CR require 3 days minimum washout (see Section 10.3.3 for lorazepam, eszopiclone, zopiclone, temazepam, zolpidem, and zolpidem CR treatment restrictions). Depot neuroleptics must be discontinued at least one treatment cycle prior to randomization.
4. Subject has suspected/confirmed Borderline Personality Disorder.
5. Subject currently has a clinically significant neurological, metabolic (including type 1 diabetes), hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, and/or urological disorder such as unstable angina, congestive heart failure (uncontrolled), or central nervous system (CNS) infection that would pose a risk

to the subject if they were to participate in the study or that might confound the results of the study. Subjects with a known history of HIV seropositivity will be excluded.

Note: Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if under control) must be discussed with the Medical Monitor before being randomized in the study.

6. Subject has evidence of any 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. In addition, subjects must not have a history of intellectual disability or persistent neurological symptoms attributable to serious head injury. Past history of febrile seizure, is not exclusionary.
7. Subject has a history of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Subjects with pituitary tumors of any duration are excluded.
8. Subject demonstrates evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation (use screening values for laboratory evaluation). Subject has a history of stomach or intestinal surgery or any other condition that could interfere with absorption, distribution, metabolism, or excretion of medications.
9. Subject has knowledge of any kind of cardiovascular disorder/condition known to increase the possibility of QT prolongation or 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.
10. Subject has family history of QTc prolongation or of unexplainable sudden death at < 50 years of age.
11. Abnormal 12-lead ECG at Screening, including:
    - QTcF > 450 ms (male subjects) or > 470 ms (female subjects)
    - QRS > 110 ms
    - PR > 200 ms
    - Second- or third-degree atrioventricular block
    - Any rhythm other than sinus rhythm, which is interpreted by the Investigator to be clinically significant
12. Subject has a history of neuroleptic malignant syndrome (NMS).
13. Subject exhibits evidence of severe tardive dyskinesia, severe dystonia, or any other severe movement disorder. Severity is to be determined by the investigator.

14. Subject has been diagnosed with type 1 diabetes, or insulin-dependent diabetics.
15. Subject who has any abnormal laboratory parameter at screening that indicates a clinically significant medical condition as determined by the investigator.
    - Subjects with fasting blood glucose at screening ≥ 126 mg/dL (7.0 mmol/L) will be excluded from the study.
    - 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 blood glucose is < 200 mg/dL. Subjects with random (nonfasting) blood glucose at screening ≥ 200 mg/dL (11.1 mmol/L) must be retested in a fasted state.
    - Subjects with HbA_{1c} > 7.0% will be excluded.
16. Subject has a prolactin concentration > 100 ng/mL at screening or have a history of pituitary adenoma.
17. Subject has a body mass index (BMI) ≥ 40 or < 18 kg/m^2 at Screening.
18. Subject has a history of non-response to an adequate (6-week) trial of three or more antidepressants (with or without mood stabilizers) during the current episode.
19. Subject is considered by the Investigator to be at imminent risk of suicide or injury to self, others, 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 month [30 days]) or Baseline.
20. Subject tests positive for drugs of abuse at screening or baseline. 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.
21. Subject has a history of hypersensitivity to more than two distinct chemical classes of drug (eg, sulfas and penicillins).
22. Subjects have received depot neuroleptics unless the last injection was at least one treatment cycle before randomization.
23. Subject requires treatment with a drug that consistently prolongs the QTc interval (see Section 23, Appendix IV).
24. Subject has received ECT within 90 days prior to randomization or is expected to require ECT during the study course.
25. Subject is currently participating, or has participated in a study with an investigational or marketed compound or device within 6 months prior to signing the informed consent, or has participated in 3 or more studies within 18 months prior to signing the informed consent.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

SEP-4199 will be supplied as matching 100 mg and 200 mg tablets each containing a fixed ratio of 85:15 (R-amisulpride:S-amisulpride). Two 100 mg tablets will be given for the 200 mg dose. Two 200 mg tablets will be given for the 400 mg dose. Two placebo tablets matching SEP-4199 active tablets will be given for the placebo dose.

Table 5: Investigational Product

Attribute	**Investigational Product**		
Product name	SEP-4199 100 mg	SEP-4199 200 mg	Matching Placebo
Dosage form	Tablets	Tablets	Tablets
Unit dose	Tablet	Tablet	Tablet
Route of administration	Oral	Oral	Oral
Physical description	Pale orange oval film-coated unmarked tablets	Pale orange oval film-coated unmarked tablets	Pale orange oval film-coated unmarked tablets
Excipients	D-Mannitol, pregelatinized starch, croscarmellose sodium, polyvinyl alcohol, magnesium stearate, hydroxypropyl methylcellulose, Macrogol 400, titanium dioxide, talc, iron oxide yellow, iron oxide red, carnauba wax		

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in one-week blister cards containing 18 oral tablets of SEP-4199 100 mg, 200 mg, or Placebo tablets (7 days + 2 extra days).

9.2.2. Labeling Description

All labeling and packaging for study drug will be based on all applicable regulatory requirements described in either United States (US) Code of Federal Regulations (CFR), CFR21, Part 312.6, Annex 13 of "The Rules Governing Medicinal Products in the European Community, Volume 4 Good Manufacturing Practice for Medicinal Products," and/or in accordance with any other local applicable regulatory requirements. Label text may include, but are not limited to, the following information:

- Protocol number
- Sponsor's name and address
- Compound/Code or name of investigational drug (if needed)
- Contents (eg number of tablets, strength)

- Investigational Drug/caution statement or New Drug statement
- Instructions for use and storage
- Blank space for study center number and date opened (if needed)
- Lot number
- Randomization number (if needed)
- Expiration date (if needed)
- Visit number (of needed)
- Unique medication number (if needed)
- Space for subject identifiers (if needed)
- Investigator information (if needed)

9.3. Study Drug Storage

SEP-4199 tablets and placebo tablets are to be stored between 15°C and 25°C (59°F and 77°F); excursions are permitted to 30°C (86°F), and away from light. The study drug storage area will be monitored for temperature. 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 screening and randomization, drug dispensation and accountability. 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 study medication unit/number to assign to a subject. Each subject will be dispensed one or two 9-day blister cards per scheduled visit, depending on the timing of the next scheduled visit (see Table 2).

The first study drug dose will be taken on Day 1. Subjects will be instructed to take their study drug as a single oral dose once a day in the morning at approximately the same time each day. Study visits will begin no later than 6 hours postdose, if possible. Study drug may be taken with or without food. Clinical site staff will interview the subject for self-report of the last 3 doses and record the date and time of each study drug administration in the source (all visits) and CRF (Visits 4 and 6 only).

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

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by

subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/CRO.

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

The IXRS will be used for the accountability of the study drug at the clinical site. The Investigator or designee will maintain the inventory 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.

The drug will not be dispensed to any person who is not a study subject under this protocol. Study drug will not be dispensed to any subject following the completion of the 6-week treatment period.

9.6. Study Drug Handling and Disposal

A drug inventory record will be supplied from Sponsor/CRO. The Investigator or designee on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned medication. The Investigator or designee is required to return all unused study drug to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of medication shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

10. TREATMENT OF SUBJECTS

10.1. Study Drug

SEP-4199 100 mg and 200 mg tablets for 200 mg and 400 mg doses will be supplied as described in Section 9.1.

Study drug tablets 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 ± 2).

10.2. Treatment Compliance

Subjects will self-report the date and time of their last 3 doses prior to each clinic visit. Site staff will record these last 3 dosing times in the CRF for Visits 4 and 6 and returned drug accountability details in IXRS for each dispensed kit upon return by subject.

10.3. Prior and Concomitant Medications and Therapies

The following information on all concomitant medication administered between Visit 1 and Visit 7 or at discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

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

Initiation of new psychotherapeutic interventions (e.g., 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.

Any medication or non-pharmacological therapy that is taken by or administered to the subject at any point during the course of this study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

10.3.1. Prior 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 randomization. Treatment with sedative hypnotics (for insomnia) is permitted during the screening period, but should be tapered as clinically appropriate to conform with and adequately prepare the subject for the protocol-specified dosing limitations applicable to these agents following randomization (see Section 10.3.3). Subjects treated with fluoxetine, or olanzapine plus fluoxetine combination must discontinue these medications at least 28 days prior to randomization. Depot neuroleptics must be discontinued at least one treatment cycle prior to randomization. Subjects treated with MAO inhibitors must discontinue these medications at least 21 days prior to randomization. All other psychotropic medication (except as described in this section), including medication and herbal supplements (eg, Gingko Biloba, Kava Kava, St. John's Wort) must be discontinued as tolerated and clinically

appropriate prior to randomization. Subjects should not be taken off their current effective medications for treatment of bipolar depression for purposes of participating in this protocol.

10.3.2. Concomitant Nonpsychotropic Medications

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during screening and after randomization 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 randomization (or be discontinued). Routine vaccines (ie, seasonal influenza, pneumonia, etc.) are allowed based on Investigator judgement. β-adrenergic antagonists used to treat stable hypertension may be continued through the screening/washout phase and post-randomization. In addition, use of non-prescription pain medications (e.g., aspirin, acetaminophen/paracetamol, ibuprofen) is allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study medication. Medications for short-term treatment of a medical condition (no more than 10 days) are allowed without consultation with the Medical Monitor provided that the medications do not consistently prolong the QTc interval (see Section 23, Appendix IV).

10.3.3. Concomitant Psychotropic/Antipsychotic Medications

Treatment with benztropine (up to 6 mg/day) will be permitted as needed for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute EPS: biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with propranolol (up to 120 mg/day) or amantadine (up to 300 mg/day) will be permitted as needed for akathisia. These allowed medications for the treatment of EPS, akathisia, and dystonia may be given in any formulation (oral, IM, or IV) as deemed appropriate by the investigator. Medications used to treat movement disorders should not be given prophylactically. Medications used for movement disorders should be tapered and discontinued prior to randomization but may be reinstituted if symptoms emerge.

In situations where anticholinergic agents or sedative/hypnotic agents (or any agents that may cause sedation) are administered, these should be taken at the same time each day and should not be taken within 8 hours of scheduled assessments. In regions that do not have the specified drugs available, similar drugs at equivalent dosages will be substituted as described in the Study Reference Manual or in consultation with the Medical Monitor.

Concomitant use of sedative hypnotics is permitted during Screening and for Weeks 1-3 (through Visit 5) at the discretion of the Investigator with the following restrictions: Lorazepam is permitted at the discretion of the Investigator up to 2 mg/day for intolerable anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per investigator judgment. 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. Continued use of the above sedative hypnotics beyond Visit 5 requires approval from the Medical Monitor.

Anxiolytics, sedatives or hypnotics should not be administered within 8 hours prior to any psychiatric assessments.

In regions where lorazepam or zolpidem or other specified medications are not available, another similar agent at equivalent doses will be permitted as specified by the Medical Monitor and/or the Study Reference Manual. Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor.

Subjects who require treatment with one or more of the restricted medications should be excluded or discontinued (as appropriate) from the study. Since the list of medications in Section 23, Appendix IV is not comprehensive, the Investigator should use medical judgment when a subject presents with a medication not on the list or consult with the Medical Monitor for clarification.

10.3.4. Prohibited Medications

Treatment with all 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 prior to randomization, whichever is longer. Subjects treated with fluoxetine or olanzapine plus fluoxetine combination must have discontinued these medications at least 28 days prior to randomization. Depot neuroleptics must have been discontinued at least one treatment cycle prior to randomization. Subjects treated with MAO inhibitors must have discontinued these medications at least 21 days prior to randomization.

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 randomization (see Section 10.3.3).

Medications that consistently prolong the QTc interval are prohibited during the study. For a list of these medications, please see Section 23, Appendix IV.

The use of herbal supplements for any reason is prohibited during trial participation. 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, and diphenhydramine (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

1. Female subjects of childbearing potential must be using and willing to continue using a highly effective form of birth control for at least 28 days prior to administration of the first dose of study drug, during the treatment period, and 2 months (60 days) after completion or premature discontinuation from the study drug. Highly effective forms of contraception include:
    - Combined estrogen and progestogen containing hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation.
    - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.

- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Women using hormonal contraception must use an additional form of contraception (eg, condom with spermicide). Because of the unacceptable failure rate of barrier (chemical and/or physical) methods, the barrier method of contraception must only be used in combination with a highly effective method. Post-coital methods of contraception are not permitted. The following is required:

2. A female subject is eligible to enter and participate in the study if she is of:
    a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant, including any female who is pre-menarchal or post-menopausal);
        – Postmenopausal females defined as being amenorrheic for greater than 2 years (or confirmed by FSH level) with an appropriate clinical profile.
        – Women who have had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy (as determined by subject's medical history).
        – Women who have not been confirmed as postmenopausal and are not surgically sterile should be advised to use contraception as outlined above under number 1.
    b. Childbearing potential, has a negative pregnancy test at screening and agrees to satisfy one of the following requirements:
        – Complete abstinence from intercourse (as part of an abstinent lifestyle) a minimum of 2 months (60 days) prior to administration of the first dose of study drug, throughout the Treatment Period, and for a minimum of 3 months (90 days) after completion or premature discontinuation from the study drug; or,
        – Established use of highly effective methods of contraception from 28 days prior to administration of the first dose of study drug, during the Treatment Period, and 2 months (60 days) after completion or premature discontinuation from the study drug. Highly effective methods of birth control are listed above in number 1).

Male Subjects

Male subject with female partner(s) of childbearing potential must ensure that their partner(s) uses the methods of contraception as outlined for female subjects above.

10.5. Guidance for Overdose

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

11. STUDY ASSESSMENTS

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

Study drug should be administered once daily in the morning at approximately the same time each day.

11.1. Demographics and Baseline Characteristics

Subject self-report will be acceptable for listing all prior and concomitant medication use, demographics, medical history, psychiatric history, and evaluation for inclusion/exclusion except where specific protocol procedures are mandated to ensure appropriate enrollment (eg, certain baseline laboratory values). All medications taken within the 30 days before screening will be recorded.

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 CRF.

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

11.2. Diagnostic Scales to Determine Study Eligibility

11.2.1. 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 (i.e., 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-CT for clinical trials (SCID-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. Further information regarding administration of the SCID-5-CT to determine study eligibility will be provided in the Study Reference Manual.

11.2.2. 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. YMRS uses operationally defined anchor points and the normal expected score is > 20. Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score).

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 YMRS scores to determine study eligibility will be provided in the Study Reference Manual.

11.2.3. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS will be administered at Screening and Baseline to determine subject eligibility. To be eligible for enrollment, subjects must have a MADRS total score ≥ 22 at Screening. 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 study participation (see Section 24, Appendix V).

The MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. The Structured Interview Guide for the MADRS (SIGMA) will be used for the administration of the MADRS assessment.

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

11.3. Efficacy Assessments

11.3.1. 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 visits as an efficacy assessment. The MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. The Structured Interview Guide for the MADRS (SIGMA) will be used for the administration of the MADRS assessment.

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

11.3.2. Clinical Global Impressions – Severity: Bipolar Version (CGI-BP-S - Depression)

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.

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.

11.3.3. Hamilton Rating Scale for Anxiety (HAM-A)

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 scale, ranging from 0 (not present) to 4 (severe/disabling). The Structured Interview Guide for the HAM-A (SIGH-A) will be used for the administration of the HAM-A.

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

11.3.4. Sheehan Disability Scale (SDS)

The SDS is a composite of three items designed to measure the extent to which three major sectors in the patient's life are impaired by depressive symptoms. This anchored visual analog scale uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability across three domains: work, social life, and family life. The patient rates the extent to which his or her 1) work, 2) social life or leisure activities, and 3) home life or family responsibilities are impaired by his or her symptoms on an 11-point visual analogue scale ranging from 0 to 10. There are verbal descriptors for the points on the scale as well as numerical scores that provide more precise levels of the verbal descriptors. The three items may be 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 SDS scores will be provided in the Study Reference Manual.

11.3.5. Quick Inventory of Depressive Symptomatology – Self-Report 16-Item (QIDS-SR16)

The QIDS-SR16 is a 16-item self-report measure of depressive symptomatology which uses a computerized assessment interface for administration. The scoring system for the QIDS-SR16 converts responses to 16 separate items into the nine DSM-IV symptom criterion domains. The total score ranges from 0 to 27. The nine domains comprise: sad mood; concentration; self-criticism; suicidal ideation; interest; energy/fatigue; sleep disturbance (initial, middle, and 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, which will take place at the site. Clinical site staff will not participate in the administration of the QIDS-SR16 after initiation.

Further information regarding administration of the QIDS-SR16, including recording scores will be provided in the Study Reference Manual.

11.3.6. EuroQoL 5-D (EQ-5D-5L)

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 EQ VAS.

The descriptive system comprises five 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 patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

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

11.4. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments as they become available. The Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct through appropriate adverse event reporting and/or escalation to the Medical Monitor.

11.4.1. Pretreatment Events and Adverse Events

Pretreatment events will be recorded from the time informed consent is provided at screening until the time of first dose administration at Day 1.

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.

11.4.2. Clinical Laboratory Tests

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

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed centrally. 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.

11.4.3. Vital Signs

Supine systolic and diastolic blood pressures, respiratory rate, pulse rate, and temperature will be measured.

After being in a supine position for ≥ 5 minutes, systolic and diastolic blood pressures, respiratory rate, pulse rate, and temperature will be collected. 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.

11.4.4. Centrally-read ECG

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 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 core lab according to established quality assurance procedures for inter/intra reader variability. Refer to Section 20, Appendix I for additional information.

To determine subject eligibility, Screening ECG may only be repeated due to technical issues.

11.4.5. Safety Scales

11.4.5.1. 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 Screening (in the past month) are not eligible and must be referred to the Investigator for follow-up evaluation.

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

11.4.5.2. 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 at post-baseline visits as an efficacy assessment.

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. YMRS uses operationally-defined anchor points and the normal expected score is > 20. Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score).

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

11.4.5.3. Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements consisting of unobtrusive observation of the subject at rest (with shoes removed) and several questions or instructions directed toward the subject. Using a severity scale ranging from 0 (none) to 4 (severe), clinicians rate dyskinesia in several body regions, including the facial area, extremities, and trunk. There are two items related to dental status, as well as three global impression items assessing overall severity, incapacitation, and the subject's awareness of abnormal movements (Guy 1976, Munetz 1988). 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 AIMS scores will be provided in the Study Reference Manual.

11.4.5.4. Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale geared toward assessment of neuroleptic-induced akathisia, though it can be used to measure akathisia associated with other drugs as well. The BARS consists of four items, including one item assessing objective restlessness, two items targeting subjective restlessness (awareness and related distress), and one global clinical assessment item. All items are anchored and utilize a 4-point scale, except for the global rating which has a 6-point scale (from absence of akathisia through severe akathisia). The subjective and objective items are summed to yield a total score. The BARS can be administered in about 10 minutes (Barnes 1989, Barnes 2003, Schooler 2000).

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

11.4.5.5. Modified Simpson-Angus Scale (SAS)

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

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

11.4.5.6. Physician Withdrawal Checklist

Assessment of potential withdrawal effects will be conducted via the Clinician administered Physician Withdrawal Checklist (PWC) at the End of Treatment visit (Day 42 ± 2, after completion of efficacy and safety assessments and procedures scheduled for this visit are completed). The PWC will be administered again at the Follow-up visit (Day 49 ± 2).

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

11.5. Pharmacokinetic Assessments

A validated enantioselective liquid chromatography-tandem mass spectrometry (LC-MS/MS) method will be used for determination of plasma R- and S-amisulpride concentrations, and an enzyme-linked immunosorbent assay (ELISA) will be used for determination of plasma prolactin concentrations.

Plasma concentrations of R-amisulpride, S-amisulpride, and prolactin will be assayed using plasma samples from blood collected according to the schedule of assessments (see Section 22, Appendix III for sample collection and handling guidelines). Blood collection date and times must be recorded.

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.

Population PK analysis methods will be used to characterize the PK/PD profiles in subjects treated with SEP-4199. Results of population PK analysis will be described in a separate report other than the clinical study report.

11.6. Study Visits and Assessments

11.6.1. 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 requirement to fast for blood sample collection for clinical laboratory tests. Subjects should be advised to bring food items if not otherwise provided by the site.

Per local clinical practice, subjects may be hospitalized for up to 7 days during the Screening period. Further need for hospitalization will require consultation with the Medical Monitor.

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

To determine subject eligibility, Screening ECG may only be repeated due to technical issues.

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 informed consent.
- Perform SCID-5-CT.
- Perform MADRS. To be eligible for enrollment, subjects must have a MADRS total score ≥ 22 (see Section 24, Appendix V).
- Administer YMRS. To be eligible for enrollment, subjects must have a YMRS total score ≤ 12.
- Administer C-SSRS (Screening/Baseline version).
- Review inclusion and exclusion criteria.
- Collect blood sample(s) for the following clinical laboratory tests:
  - Hematology and Serum Chemistry (If possible, subjects should fast for at least 8 hours [no food after midnight] to avoid potential for retest.)
  - Serum Thyroid Stimulating Hormone
  - Serum Follicle Stimulating Hormone (Female Subjects)
  - Serum β-hCG (Female Subjects of childbearing potential)
  - Serum prolactin
  - Hemoglobin A1c (HbA1c)
  - Lipid Panel
  - Serum Insulin
  - high sensitivity (hs) C-reactive Protein
- Collect blood sample for Hepatitis B/C testing.
- Collect blood sample for R- and S-amisulpride PK and plasma prolactin analysis.
- Collect urine sample for urine drug screen and urinalysis.
- Record demographics.
- Record medical history.
- Record psychiatric history and mental status. 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 prior and concomitant medications.
- Record 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.
- Perform 12-lead ECG.
- Schedule next visit.

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

11.6.2.1. Baseline: Visit 2 (Day -1)

Per local clinical practice, subjects may be hospitalized for up to 7 days during the first week of treatment with double-blind study drug. Further need for hospitalization will require consultation with the Medical Monitor.

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

- Review inclusion and exclusion criteria.
- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours [no food after midnight].):
  - Hematology and Serum Chemistry
  - Serum prolactin
  - Hemoglobin A1c (HbA1c)
  - Lipid Panel
  - Serum Insulin
  - hs C-reactive Protein
- Collect blood sample for R- and S-amisulpride PK and plasma prolactin analysis.
- Collect urine sample for urine drug screen, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Record prior and concomitant medications.
- Record 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 24, Appendix V).
- Administer HAM-A.
- Administer YMRS. To be eligible for enrollment, subjects must have a YMRS total score ≤ 12.

- Administer SDS.
- Administer QIDS-SR16.
- Administer AIMS.
- Administer BARS.
- Administer Modified SAS.
- Administer C-SSRS (Since Last Visit version).
- Administer CGI-BP-S.
- Administer EQ-5D-5L.
- Perform physical examination.
- Perform neurological examination.
- Record weight.
- Record waist circumference.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- 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 the next visit and to bring back all used/unused study drug and packaging to the next visit.

11.6.2.2. 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.
- Administer YMRS.
- Administer QIDS-SR16.
- Administer AIMS.
- Administer BARS.

- Administer Modified SAS.
- Administer C-SSRS (Since Last Visit version).
- Administer CGI-BP-S.
- Record prior and concomitant medications.
- Record adverse events.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Perform 12-lead ECG.
- Ask subject the date and time of their last 3 doses of study drug and record in the source.
- Collect used/unused study drug and packaging.
- Perform study drug accountability.
- Dispense study drug.
- Instruct subject to dose once daily in the morning 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.

11.6.2.3. Visit 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.
- Administer YMRS.
- Administer QIDS-SR16.
- Administer AIMS.
- Administer BARS.
- Administer Modified SAS.
- Administer C-SSRS (Since Last Visit version).
- Administer CGI-BP-S.
- 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 R- and S-amisulpride PK and plasma prolactin analysis.
- Collect urine sample for urine drug screen, urinalysis, and urine β-hCG (female subjects of childbearing potential).
- Ask subject the date and time of their last 3 doses of study drug and record in the source and the CRF.
- Collect used/unused study drug and packaging.
- Perform study drug accountability.
- 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.

11.6.2.4. 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.
- Administer YMRS.
- Administer QIDS-SR16.
- Administer AIMS.
- Administer BARS.
- Administer Modified SAS.
- Administer C-SSRS (since last visit version).
- Administer CGI-BP-S.
- Record prior and concomitant medications.

- Record adverse events.
- Obtain vital signs, including orthostatic changes in blood pressure and heart rate.
- Perform 12-lead ECG.
- Ask subject the date and time of their last 3 doses of study drug and record in the source.
- Collect used/unused study drug and packaging.
- Perform study drug accountability.
- 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 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.

11.6.2.5. 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 to administer the morning dose prior to the next clinic visit.

11.6.3. End of Treatment/Early Termination: Visit 6 (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:

- Collect blood sample(s) for the following clinical laboratory tests (Subjects must have fasted for at least 8 hours [no food after midnight].):
  - Hematology and Serum Chemistry
  - Serum prolactin
  - Hemoglobin A1c (HbA1c)
  - Lipid Panel
  - Serum Insulin
  - hs C-reactive Protein
- Collect blood sample for R- and S-amisulpride PK and plasma prolactin analysis.
- Collect urine sample for urine drug screen, urinalysis, and urine β-hCG (female subjects of childbearing potential).

- Administer MADRS.
- Administer HAM-A.
- Administer YMRS.
- Administer SDS.
- Administer QIDS-SR16.
- Administer AIMS.
- Administer BARS.
- Administer Modified SAS.
- Administer PWC.
- Administer C-SSRS (Since Last Visit version).
- Administer CGI-BP-S.
- Administer EQ-5D-5L.
- 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.
- Perform 12-lead ECG.
- Ask subject the date and time of their last 3 doses of study drug and record in the source and CRF.
- Collect used/unused study drug and packaging.
- Perform study drug accountability
- Schedule follow-up visit.

11.6.4. Follow-up: Visit 7 (Day 49 ± 2)

All subjects will have a follow-up visit 7 days after their last study drug dose. 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.
- Record weight.
- Record waist circumference.
- 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 R- and S-amisulpride PK and plasma prolactin analysis.
- Collect urine sample for urine drug screen, 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 pre-treatment events. Those that occur after administration of study drug are considered AEs. Pre-treatment 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 as 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 pretreatment event or an AE that meets one or more of the following criteria:

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

The term “severe” is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3); the event itself, however, may be of

relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

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

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

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) will be recorded as the AE.

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 ECG and laboratory reports and initial and date on all pages, or other acceptable documentation process approved by the Sponsor. Laboratory test and ECG 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) and abnormal ECG results. 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. Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. 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 the samples taken after dosing, during the study, and/or at the Follow-Up Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized.

If a subject experiences symptoms or ECG findings suggestive of an arrhythmia during the study, the subject should be evaluated by a cardiac specialist. If such an arrhythmia is detected during the study and is thought to be immediately life-threatening (eg, torsades de pointes [TdP]), the subject is to be treated immediately following the site's standard emergency

procedures. An SAE will be reported, and the subject discontinued from the study drug. Emergency resuscitative equipment must be available at the site.

In addition, subjects will be monitored throughout the study for clinical risk factors of TdP, such as electrolyte imbalances, bradycardia, sustained tachycardia and syncope. If a subject experiences such an adverse event, it will be managed immediately and followed until resolution.

Subjects who, at any study visit post-baseline have a QTcF value greater than 500 ms or who have a > 60 ms increase in QTcF from baseline will be discontinued from the study drug and followed until the event resolves; in addition, an adverse event will be reported.

Subjects who develop adverse events of amenorrhea, gynecomastia, or galactorrhea are to be discontinued from the study drug.

12.3. Collection and Recording of Adverse Events

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

All pre-treatment events and AEs must be recorded on the CRF.

Pre-treatment events will be recorded from the time informed consent is provided at screening until just prior to first study drug dose administration at Day 1. AEs will be recorded beginning after first study drug dose administration at Day 1 until the follow-up visit at Day 49.

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 drug, outcome, and causal relationship to the study drug. Definitions for severity, frequency, action taken with the study drug, outcome, and causal relationship to the study drug 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 drug:

- **Dose Not Changed**
- **Drug Withdrawn – Study drug stopped permanently.**
- **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 drug:

- **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 AE should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

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

12.4. Immediately Reportable Events

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

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of an SAE that occurs in a study subject up to and including the final follow-up, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs "spontaneously" to the Sponsor 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.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to the Sponsor PPD-PVG within 24 hours of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor PPD-PVG provides the SAE form used to report SAEs.

SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Principal Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

The appropriate PVG group must be contacted immediately upon first knowledge of the incident. The immediate report should be made by the Investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE or pregnancy.

Sunovion will review all SAE reports to determine if any SAEs are suspected unexpected serious adverse reactions (SUSARs).

All fatal or life-threatening SUSARs must be reported as soon as possible, but no later than 7 days after the sponsor first becomes aware of the reaction. Any additional relevant information must be sent within and additional 8 days of the clock date. All non-fatal or non-life-threatening SUSARs must be reported as soon as possible but no later than 15 days after the sponsor first becomes aware of the reaction. Sponsor safety reporting group will notify the applicable Regulatory Agencies of all SUSARs.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through the final follow-up visit 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 return promptly/within 48 hours of the first notification of pregnancy to the study center and undergo a serum/urine pregnancy test, as confirmation of pregnancy. Every effort will be made to follow-up all pregnancies, including those in the female partner of male subjects, until resolution (ie, termination [voluntary or spontaneous] or birth), providing the volunteers consent to follow-up.

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 by subject (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 drug.

Subjects who, at any study visit post-baseline have a QTcF value greater than 500 ms, who have a > 60 ms increase in QTcF from baseline, or who experience a life-threatening arrhythmia will be discontinued from the study drug and followed until the event resolves; in addition, an adverse event will be reported.

Subjects who develop adverse events of amenorrhea, gynecomastia, or galactorrhea are to be discontinued from the study drug. The reason for discontinuation and information on the epoch will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

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

Subjects who discontinue prior to Visit 6 (Day 42 [± 2]) will undergo procedures and assessments scheduled for Visit 6 (Day 42 [± 2]) at the time of early discontinuation (see Section 11.6.3).

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 be required to return for a final study assessment 7 days after their last dose of study drug (ie, follow-up) and be provided with access to standard care.

15. STATISTICS

The comprehensive statistical analysis plan (SAP) will provide details on the statistical methods planned for this study and will be finalized prior to the US and Europe cohort unblinding.

15.1. Sample Size

A total sample size of 279 evaluable subjects in US and Europe (93 per treatment group: SEP-4199 200 mg/day, SEP-4199 400 mg/day, and placebo) with a global 2-sided alpha of 0.05 will provide about 90% power to reject at least 1 truly significant comparison and about 75% power to reject both truly significant comparisons using the truncated Hochberg ($\gamma = 0.9$) procedure, assuming treatment effect sizes of 0.44 for both doses of SEP-4199. The effect sizes were selected considering the data from the completed lurasidone bipolar depression study (Loebel 2014). This effect size corresponds to a treatment difference of -3.85 for a SEP-4199 dose with a common standard deviation of 8.745 on the MADRS scale change from baseline at Week 6. An upward adjustment of approximately 5% is used to compensate for information lost due to subjects who are randomized and do not provide any postbaseline primary efficacy data. The total sample size will be approximately 294 randomized subjects (or N = 98 subjects per treatment group).

For the secondary efficacy endpoint, assuming the 93 subjects per treatment arm, the study will have 71% power to reject at least one truly significant comparison within the CGI-BP-S family using the regular Hochberg procedure, given a treatment difference of -0.47 for a SEP-4199 dose with a common standard deviation of 1.24 on the CGI-BP-S change from baseline at Week 6. The correlation between the primary and the secondary endpoint is assumed to be 0.8 for each treatment arm.

The sample size was calculated using the Mediana package version 1.05 within R version 3.4.2 (R Core Team 2017).

The sample size for the Japanese cohort (45 total [N = 15 subjects per group], including 9 dropouts) provides more than 80% probability to have a treatment difference point estimate greater than zero for the MADRS.

15.2. Analysis Populations

Each population below will be created for both the US and Europe cohort and the Japanese cohort.

Intention-to-Treat Population: The intention-to-treat (ITT) population will consist of subjects who are randomized. Subjects are included in the ITT population regardless of any protocol deviations. Subjects will be analyzed according to their randomized treatment group. The ITT population is the primary population for all efficacy analyses.

Per Protocol Population: These are all ITT subjects who have no important protocol deviations that may affect the interpretation of the primary efficacy endpoint as defined in Section 15.3.3. Subjects in the Per Protocol population will be analyzed according to their randomized treatment group.

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 the predominant treatment received. The 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.

Pharmacokinetic (PK) Population: The PK population includes the Safety population subjects who have at least 1 valid postdose PK concentration value without protocol deviations or events with the potential to affect PK. The PK analysis will be based on the PK population.

15.3. Data Analysis

In general, all analyses of the Japanese cohort are descriptive in nature and will be reported separately from the US and Europe cohort, unless otherwise specified.

Descriptive summaries will be provided where appropriate for each of the endpoints. In general, summaries will be presented by treatment arm within a population.

In general, continuous outcomes will be summarized for the number of subjects, mean, 95% CI for the mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. For categorical outcomes, the number and percentage of subjects will be presented.

All statistical inference analyses will be performed with 2-sided tests at a significance level of 0.05, unless otherwise specified.

In general, for analyses of change from baseline, baseline will be defined as the last non-missing measurement collected up to and including the day of first dose of study medication. Baseline data will be presented for all subjects by treatment arm.

All data from the CRFs, as well as any derived variables, will be presented in subject data listings. Unscheduled measurements will be included in the listings and will not be included in summary tables, unless specified otherwise.

SAS® software Version 9.4 or higher will be used for all analyses.

15.3.1. Subject Disposition

The total number of screened subjects, the number of subjects who are screen failures, and the number of subjects randomized will be presented. The number and percentage of subjects who were randomly assigned to treatment and dosed and not dosed, who were included in each population will be summarized. The number and percentage of subjects who complete and discontinue study drug will be summarized, along with reasons for study drug discontinuation. Subject disposition will be displayed by each treatment arm and overall.

15.3.2. Drug Exposure and Compliance

Drug exposure and compliance will be summarized by treatment and overall for the Safety and ITT populations.

At each visit, prior to dispensing study medication, previously dispensed study medication will be retrieved and assessed by tablet count. The total number of doses between each treatment visit and overall for the entire study will be calculated for each subject. Compliance will be based on the number of doses expected to be taken.

For subjects who discontinue study drug early, the last dose date will be the endpoint from which the scheduled number of doses will be calculated. For subjects who are lost to follow-up, and for whom the last dose date is unknown, the last contact date will be used.

Compliance will be assessed by visit and overall, both continuously (mean percentage) and categorically (compliant vs. non-compliant, non-compliant < 75% and non-compliant > 125%, and subjects with any missing compliance). Treatment compliance will also be presented in a data listing.

Exposure duration will be calculated using the number of days from the first dose through the last dose of study medication, inclusive. Exposure will be summarized both continuously overall and categorically (≥ 4 days, ≥ 7 days, ≥ 14 days, etc.) by planned visit days.

15.3.3. Important Protocol Deviations

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

- Did not meet inclusion/exclusion criteria
- Received any disallowed concomitant medication
- Had compliance < 75% or > 125%
- Other

Additional IPDs may be identified from clinical review of Investigator comments or other data. Individual IPDs will be presented in a data listing. The number and percentage of subjects in the ITT population with IPDs will be summarized by type of deviation and randomized treatment group.

15.3.4. Demographic and Baseline Characteristics

Summaries for demographic characteristics and psychiatric history will be presented by treatment group and overall for the ITT, PP and Safety populations. Demographic characteristics include age (in years), age categories (< 55 years and ≥ 55 years), gender, race, ethnicity, country, geographic region (US, Europe and Japan), weight, height, body mass index, waist circumference as well as the MADRS total score, and the CGI-BP-S depression score at baseline.

Summaries of other current psychiatric disorders present will include DSM-IV codes and Medical Dictionary for Regulatory Activities (MedDRA®), Version 20.1 or higher, preferred terms and will be provided for the ITT, PP and Safety populations.

The medical history of each subject will be coded by system organ class (SOC) and preferred term (PT) using the MedDRA, Version 20.1 or higher. The number and percentage of subjects

with medical history findings in each SOC and PT will be summarized by treatment group and overall for the Safety and ITT populations.

15.3.5. Efficacy Analyses

In general, all efficacy analyses of the Japanese cohort are descriptive in nature, any additional analysis details will be provided in the SAP.

15.3.5.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from baseline in the MADRS total score at Week 6.

The primary efficacy estimand is defined as the efficacy of each SEP-4199 dose over placebo for 6 weeks, calculated as the difference in the primary efficacy endpoint between each SEP-4199 treatment group and the placebo treatment group in the ITT population. This estimand, which will only include those subjects who participate in sites located in US and Europe, provides an estimate of the efficacy of each SEP-4199 dose over placebo, should a subject be able to tolerate and adhere to treatment for 6 weeks.

The efficacy of SEP-4199 in terms of the MADRS total score will be evaluated using the following two null hypotheses:

> H1: There is no difference in mean change from baseline at Week 6 on the MADRS total score in the SEP-4199 200 mg treatment arm compared to Placebo.
>
> H2: There is no difference in mean change from baseline at Week 6 on the MADRS total score in the SEP-4199 400 mg treatment arm compared to Placebo.

The alternative hypothesis for each of the null hypotheses is that there is a difference, respectively. If at least, one of the primary comparisons demonstrate a significant result, the study will be considered positive.

The primary efficacy endpoint will be analyzed for the ITT population by means of an MMRM analysis, with change from baseline in the MADRS total score as the response variable and with factors for treatment group, visit, region, baseline MADRS total score, and the treatment-by-visit interaction. This analysis method makes a missing at random (MAR) assumption to the missing primary efficacy endpoints. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance matrix will be used for the within-subject correlation. A robust sandwich estimator for the standard error of the fixed effects (Diggle 2002) along with a spatial exponential or a spatial power covariance structures will be assumed sequentially in case of a convergence problem. The first covariance structure to yield convergence will be used in the analysis.

The Least Square (LS) mean treatment differences (each SEP-4199 group 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 MMRM.

Multiplicity adjustment to control the global familywise Type I error rate at 5% is described in Section 15.3.5.4.

The normality assumption underlying the primary MMRM model will be assessed graphically. Details will be provided in the SAP.

An additional exploratory analysis with the Japanese cohort primary efficacy data will be performed by replacing region (US, EU) with region (US, EU, and Japan) in the primary MMRM model. The Japanese cohort alone will also be analyzed using an MMRM method. Details will be provided in the SAP.

15.3.5.1.1. Sensitivity Analyses

To address early dropouts under the assumption of missing not at random (MNAR), a pattern-mixture model (PMM) using a placebo-based multiple imputation method and a pattern mixture model using multiple imputations with penalties **(**ie**,** tipping point analysis by 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 based on the ITT population.

MADRS total score change from baseline values over time for dropouts and for completers will be plotted by visit dropout and reason for discontinuation categorizations to assess the impact of dropouts on the efficacy endpoints. Subjects will be grouped by the visit at which they had their last efficacy score measured. This will result in five categories of subject discontinuation: Week 1 dropouts, Week 2 dropouts, Week 4 dropouts, Week 6 dropouts and Completers.

15.3.5.1.2. Supportive Analyses

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) on the ITT population as supportive analysis. The model will include terms for treatment, region and baseline MADRS total score as covariate. The LS mean of treatment differences (each SEP-4199 group minus placebo), their 2-sided 95% CIs, and the associated p-values will be obtained from the model.

The primary MMRM analysis will be repeated for the PP population to examine the impact of protocol deviations.

A supplementary analysis of the primary efficacy of SEP-4199 will be conducted to explore the dose response relationship using the Multiple Comparison Procedure – Modelling (MCP-Mod) methodology. Possible dose response shapes to assess include linear, quadratic, Emax, and sigmoidal Emax. The best model fit will be selected using the minimum Akaike information criterion out of the statistically significant multiple contrast tests based on optimal contrast coefficients. Once the best model is selected, target dose(s) of interest including the minimum effective dose will be explored.

Details will be provided in the SAP for any additional supportive analyses.

15.3.5.2. Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoint, the CGI-BP-S score, will be analyzed by the MMRM method described for the primary efficacy endpoint using the ITT population with the appropriate baseline used as the covariate.

The secondary endpoint will be tested once at least one primary endpoint is deemed significant using a mixture-based gate-keeping approach to control the global familywise Type I error rate. The details are described in Section 15.3.5.4.

The MMRM analysis will be repeated using the PP population for the secondary endpoints. Both endpoints will also be analyzed using an ANCOVA model with treatment, region as fixed effects and appropriate baseline as a covariate for the ITT population.

Sensitivity analyses similar to the primary endpoint will be repeated for the secondary efficacy endpoint. Details will be provided in the SAP.

Details will be provided in the SAP for the secondary efficacy endpoint analyses and any additional supportive analyses.

15.3.5.3. Other Efficacy Endpoint Analyses

All other efficacy endpoints will be performed using the ITT population.

The HAM-A and the QIDS-SR16 total scores will be analyzed by the MMRM method described for the primary efficacy endpoint with the appropriate baseline as the covariate.

The HAM-A, the QIDS-SR16, the SDS, and the EQ-5D-5L total scores will be analyzed using an ANCOVA model with treatment, region as fixed effects, and appropriate baseline as a covariate.

A MADRS total score responder is defined as achieving a $\geq$ 50% reduction from the baseline total score. The MADRS total score responder proportions at Week 6 will be compared among the 3 treatment arms using logistic regression. This model will include treatment and region as fixed effects and baseline MADRS score as a covariate.

The log rank testing method will be used to test for differences among the treatments for time to MADRS responder response. Subjects discontinuing the study and those completing the study without meeting the criteria for MADRS response will be censored at the date of treatment discontinuation or, if unknown, the date of last contact. The analysis will be supplemented with Kaplan-Meier curves to illustrate the differences among the three treatments.

A cumulative distribution curve for all treatment groups will be presented, plotting the cumulative percent of MADRS responders versus the change from baseline in MADRS total score at Week 6.

Remission incidence rates will be analyzed similarly to the MADRS responder analysis.

Details will be provided in the SAP for the other efficacy endpoint analyses and any additional supportive analyses.

15.3.5.4. Adjustment for Multiplicity

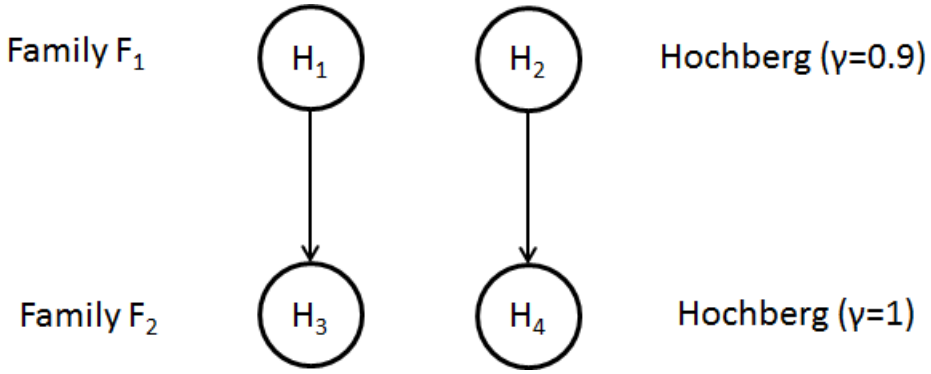
A mixture-based gatekeeping approach using the truncated Hochberg ($\gamma = 0.9$) will be used to control the global FWER at 5% for the primary (E1) and secondary endpoint (E2) (Dmitrenko 2017). Using this method, a hypothesis is testable in a latter family only if the hypothesis in the former family associated with the same dose level is rejected.

The hypotheses associated with the primary and the secondary endpoint will be grouped into 2 hierarchical families as seen in Figure 2.

- Family F1: SEP-4199 200 mg/day versus placebo (H_1), and SEP-4199 400 mg/day versus placebo (H_2), based on change from baseline in MADRS total score at Week 6 (E1)

- Family F2: SEP-4199 200 mg/day versus placebo (H_3), and SEP-4199 400 mg/day versus placebo (H_4) based on change from baseline in CGI-BP-S depression score at Week 6 (E2)

Figure 2: Hierarchy of Testing for Primary and Secondary Endpoints



The mixture-based gatekeeping procedure will be performed in 2 steps:

- Step 1: The SEP-4199 vs placebo comparisons for E1 (hypotheses H_1 and H_2) will be performed using a truncated Hochberg ($\gamma = 0.9$) test.
- Step 2: The SEP-4199 vs placebo comparisons for E2 (hypotheses H_3 and H_4) will be performed using a regular Hochberg test only when the corresponding comparisons from Step 1 are rejected. For example, H_4 is tested only if H_2 is rejected.

The primary efficacy analysis will be repeated for the PP population to provide additional information on the robustness of the primary efficacy results. The Hochberg procedure will not be used for the PP population.

15.3.5.5. Efficacy Subgroup Analyses

Subgroups, including but not limited to country, gender (male, female), race (White and Non-white for the statistical model, the rest of categories, Black/African American, Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, Other, will also be summarized), ethnicity (Hispanic and non-Hispanic), age groups, and bipolar I diagnosis subtype (rapid cycling and non-rapid cycling) will be detailed in the SAP. For the primary and the secondary efficacy endpoints, analysis will be performed for the subgroups with the same MMRM with additional terms for the subgroup, subgroup-by-treatment interaction, subgroup by visit interaction and subgroup-by-treatment-by visit interaction using the ITT population. For the country analyses, region will be replaced with country. Summary statistics and the LS mean treatment differences (each SEP-4199 group minus placebo) of change from baseline at Week 6, their 2-sided 95% CIs, and the associated p-values will be provided as well as the p-value for the treatment-by-subgroup interaction.

15.3.6. Safety Analyses

In general, safety analysis will be repeated for the Japanese cohort using descriptive statistics.

15.3.6.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. AEs are untoward medical occurrences:

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

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

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

The following conventions will be followed in summarizing AEs:

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

Summaries of SAEs, non-serious AEs with a 5% cutoff, and AEs leading to study drug discontinuation will be provided. Additional summaries may be provided using AEs of special interest.

A listing of all AEs will be provided, as well as a listing of deaths, a listing of SAEs, a listing of AEs leading to study drug discontinuation and a listing of pre-treatment untoward medical events.

15.3.6.2. Treatment-Emergent Mania

Number and percentage of patients with treatment-emergent mania, as assessed by the YMRS total score of ≥ 16 on any 2 consecutive visits or at the final assessment, or an AE of mania or hypomania will be summarized by treatment group. Mania incidence rates will be analyzed similarly to the MADRS responder analysis. The mania indicator will be set to 1 if the subject exhibits post-baseline mania, and 0 if the subject does not experience post-baseline mania and has at least 1 non-missing post-baseline YMRS total score, and missing otherwise.

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

15.3.6.3. Clinical Laboratory Assessments

All summaries involving clinical chemistry, hematology, and urinalysis tests will be based on the Safety population.

Descriptive statistics for absolute value and change from baseline will be displayed at each visit by treatment group for each chemistry, hematology, and urinalysis laboratory test measured on a continuous scale. Serum prolactin values will be summarized by treatment group and gender.

Nonparametric rank ANCOVA with adjustments for baseline value will be applied to change from baseline in serum prolactin, lipids, glucose, for comparison between each SEP-4199 group and placebo. Serum prolactin will be assessed separately by gender.

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

The number and percentage of subjects with a Markedly Abnormal Post-baseline Laboratory value (MAPLV, to be defined in the SAP) for select parameters will be summarized by post-baseline visit and overall for each treatment group.

The data listings for laboratory parameters will flag values outside of the reference range.

15.3.6.4. ECGs

All ECG summaries will be based on the Safety population. ECG parameters will include ventricular heart rate, PR interval (msec), RR interval (msec), QRS duration, QT interval, and corrected QT intervals (Bazett's QT_cB and Fridericia's QT_cF).

Summary statistics for the actual values and change from baseline will be presented by treatment group at each time point for each parameter.

Shifts from baseline will be produced by treatment group to show the number and percentage of subjects for changes in overall ECG assessments at post-baseline.

The number and percentage of subjects with elevated QTc intervals (> 450 msec for males, > 470 msec for females, > 480 msec and > 500 msec for males or females) and changes from baseline in QT_c intervals ≥ 30 msec, but < 60 msec and ≥ 60 msec will be summarized by treatment group. A listing displaying ECG values for subjects with at least one prolonged QT_c will also be produced.

For other ECG parameters, subjects will be classified as normal or abnormal (see SAP for details). For abnormal ECG parameter reporting, counts and percentages of subjects will be presented by treatment group.

For these categorical analyses, the percent of subjects will be based on the number of subjects with at least one non-missing post treatment value. Any early termination visit or unscheduled ECG that occurs after first dose will be included for these posttreatment summaries.

Electrocardiogram clinical interpretation of ECG findings will be presented in data listings.

15.3.6.5. Vital Signs

All vital sign summaries will be based on the Safety population.

Summary statistics for actual values and the change from baseline will be presented by treatment group, for each time point and each parameter.

Nonparametric rank ANCOVA with adjustments for baseline value will be applied to change from baseline in weight and BMI for comparison between each SEP-4199 group and placebo.

The number and percentage of subjects with Markedly Abnormal Post-baseline Vital Signs (MAPVS, defined in the SAP) will be presented at each post-baseline visit and overall. Included will be subjects having experienced MAPVS at least once post-baseline.

The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized by treatment by time point and overall. Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after the subject had been standing for at least 2 to 4 minutes, compared to the systolic and diastolic blood pressures measured in the supine position, respectively. Orthostatic tachycardia is defined as a heart rate increase of at least 20 beats per minute (bpm) and a heart rate > 100 bpm after the subject was standing for at least 2 to 4 minutes, compared to the heart rate measured in the supine position.

15.3.6.6. Movement Disorder Measures

Descriptive statistics for absolute value and change from baseline will be displayed at each visit by treatment group for the AIMS, BARS and Modified SAS total scores.

Each total score will be analyzed using MMRM and ANCOVA based on the change from baseline to Week 6 similar to the primary efficacy endpoint, with the respective baseline values as covariate.

Any additional analysis details will be provided in the SAP.

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

Frequency and severity of suicidal ideation or suicidal behavior in the C-SSRS will be summarized at each visit and overall by treatment group. Responses to each of the questions will be listed.

15.3.6.8. Neurological and Physical Examination

Findings from the physical and neurological examinations will be presented as follows: pre-existing clinically significant conditions recorded as medical history will be summarized, and new clinically significant conditions recorded as an AE.

15.3.6.9. Concomitant Medications

All medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical) classification (ie, ATC level 3) and PT according to the World Health Organization drug dictionary (WHO-DD) ATC classification level 3 and Preferred Term (PT) (1 Sept 2017 or more recent).

Any medications taken during the course of the study, with a start date on or after the date of the first dose of study drug and on or before the date of the last dose of study drug; or with a start date prior to, and an end date on or after, the date of the first dose of study drug, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the date of the first dose of study drug will be considered prior medications. Medications that started after the date of the last dose of study drug will not be considered concomitant, but will be considered post-treatment.

A detailed listing of prior, concomitant, and post medications taken by subjects will be provided. The number and percentage of subjects using concomitant medication will be summarized by treatment group by ATC and PT using the Safety population. Subjects with multiple uses of a medication will be counted only once for a given drug class or PT.

15.3.6.10. Safety Subgroup Analyses

Select safety data may be presented by geographic region, age, gender, and/or race subgroups. Details will be provided in SAP.

15.3.7. Pharmacokinetic Analysis

All PK analysis will be performed using the PK population.

The PK collection times and deviations and/or any values excluded from analysis will be presented in data listings. Any plasma concentration summary statistics below the limit of quantification will be represented by “BLQ” in tables and listings.

Concentrations at each scheduled sample collection time point will be summarized descriptively (n, mean, median, minimum, maximum, coefficient of variation [CV] and if appropriate, geometric mean and geometric CV [GCV]). All PK summaries will be presented by dose.

The complete methodology and results of the population pharmacokinetic/pharmacodynamic analyses will be reported separately from the SAP as an appendix to the CSR.

The relationship between SEP-4199 PK and plasma prolactin will also be explored as an appendix to the CSR.

15.3.8. Interim Analysis

There is no planned interim analysis for the primary analysis of the US and EU subjects.

Following completion of the US and Europe cohort, a US and Europe only unblinding will be performed to analyze all related data. The primary analysis will be based on US and EU subjects. All Type I error will be used during this analysis.

Additional analyses will be performed after completion of the Japanese cohort.

15.3.9. Treatment of Missing Data

If one or more items of the MADRS total score are missing at a visit, the total score will be set to missing. For other scales with missing items, the total or subtotal score will be defined in the SAP.

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

Details of incomplete/missing dates for any endpoint 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) will be recorded in the subject's electronic CRF. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11 (Medidata Rave). Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

16.2. Computerized Systems Used for Source Data

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

Table 6: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Informed consent	A
Inclusion/Exclusion Criteria Review	A
Randomization	B
Dispense Study Drug	B
Administer Study Drug	A/B
Study Drug Accountability	B
Prior/Concomitant Medications	A
Pretreatment Event Monitoring	A
Adverse Event Monitoring	A
Medical History	A
Psychiatric History/Mental Status	A/C
Structured Clinical Interview for DSM-5-Clinical Trial Version (SCID-5-CT)	C
Physical Examination	A
Height	A
Weight (Including Body Mass Index)	A
Waist Circumference	A
Vital Signs	A
12-Lead Electrocardiogram (ECG)	A
Montgomery-Asberg Depression Rating Scale (MADRS)	C
Hamilton Rating Scale for Anxiety (HAM-A)	C
Columbia-Suicide Severity Rating Scale (C-SSRS)	C

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

Protocol Step	Computerized System Type or Description
Young Mania Rating Scale (YMRS)	C
Sheehan Disability Scale (SDS)	C
Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR16)	C
Abnormal Involuntary Movement Scale (AIMS)	C
Barnes Akathisia Rating Scale (BARS)	C
Modified Simpson-Angus Scale (SAS)	C
Clinical Global Impression – Bipolar Version-Severity of Illness (CGI-BP-S)	C
Physician Withdrawal Checklist	C
EuroQoL 5 dimensional questionnaire (EuroQoL-5D-5L)	C
Hepatitis B/C	A
Urine Drug Screen	A
Serum Thyroid Stimulating Hormone	A
Serum Follicle Stimulating Hormone (Female Subjects)	A
Serum β-hCG (Female Subjects of child-bearing potential)	A
Urine β-hCG (Female Subjects of child-bearing potential)	A
Hematology, Serum Chemistry, and Urinalysis	A
Serum Prolactin	A
Hemoglobin A1c (HbA_{1c})	A
Lipid Panel	A
Serum Insulin and C-reactive Protein	A
R- and S-Amisulpride Pharmacokinetic and Plasma Prolactin Blood Sample	A
Statistical analysis	SAS® software, version 9.4 or higher

Abbreviations: EDC = electronic data capture; eCOA = electronic clinical outcome assessments; IXRS = interactive response system; PK = pharmacokinetic(s).
A = EDC; B = IXRS; C = eCOA.

16.3. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with ICH GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.4. Audits

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

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of center facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center SOPs, protocol, ICH GCP and local regulations. The 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, CRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

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

16.6. Clinical Laboratory Certification and Normal Values

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

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

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

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

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

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

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

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

17.2. Institutional Review Board/Independent Ethics Committee

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

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

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

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

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

17.3. Informed Consent

The 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 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 CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent 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 uphold the subjects confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

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

17.5. Protocol Amendments and Emergency Deviations

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

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

17.6. Records Retention

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

17.7. Inspection of Records

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

17.8. Financial Disclosure

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

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

17.9. Publication Policy

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

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

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

17.10. Compensation

If subjects have any adverse event or injury directly resulting from the study medications or procedures, the Sponsor will appropriately compensate 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-HT7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology (Berl). 2009;205:119-28.

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.

Diggle PJ, Heagerty P, Liang KY, and Zeger SL. The analysis of Longitudinal Data. Oxford, England: 2nd Edition. Oxford University Press, 2002.

Dmitrienko A, Pulkstenis E Eds. Clinical Trial Optimization using R. CRC Press 2017.

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.

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.

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.

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.

Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sachs G. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014 Feb;171(2):160-8.

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.

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

R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical. Computing, Vienna, Austria. https://www.R-project.org/.

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.

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

19. INVESTIGATOR APPROVAL

I have read the protocol SEP380-201, Version 2.00, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SEP-4199 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 Dainippon Pharma Co., Ltd., 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 [IQVIA] 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 at least 5 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

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

4. Data Standardization

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

21. APPENDIX II. CLINICAL LABORATORY TESTS

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)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

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

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

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

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

SEROLOGY PANEL: Hepatitis B Ag and Hepatitis C Ab

RENAL FUNCTIONING: Creatinine clearance (Calculated GFR)

OTHER TESTS: Follicle-stimulating Hormone (FSH; female subjects only), Serum Pregnancy (β-hCG) (female subjects only), Urine Pregnancy Test (female subjects only), HB A1C, 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.	R- and S-Amisulpride PK and Plasma Prolactin Blood Sample Collection Times:
1	-22 to -2	Baseline prolactin
2	-1	Predose
4	14 (± 2)	Postdose*
6	42 (± 2)	Postdose*
7	49 (± 2)	Follow-up**

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

COLLECTION REQUIREMENTS:

Collect 4 mL blood sample into a K_2EDTA (ethylenediaminetetraacetic acid) treated Vacutainer® (or equivalent) tube at each time point. Invert gently 8 to 10 times to mix well. Keep the blood collection tube on wet ice prior to centrifugation, and centrifuge for 10 minutes at 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 -70°C 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 R- and S-amisulpride concentration measurements, and Set-2 samples will be shipped to another lab for prolactin concentration measurement.

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

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

24. APPENDIX V. 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		-	-