Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

SEP-363856

REVISED CLINICAL PROTOCOL

Protocol Title: A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Flexible Doses of SEP-363856 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder

Protocol Lay Person Short Title: A Trial of the Safety and Efficacy of Flexible Doses of SEP-363856 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder

Protocol No. 382-201-00001
IND No. 161135
EU Trial No. 2022-500538-27-00

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	2/3
Clinical Trial Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety Fax: CCI [redacted] E-mail: CCI [redacted]
Amendment 5 Approval:	22 Jul 2025
CCI [redacted]	
Approval:	12 May 2022

Table of Contents

Table of Contents 2
List of In-text Tables 8
List of In-text Figures 9
List of Abbreviations 10
1 Protocol Summary 13
1.1 Synopsis 13
1.2 Schema 24
1.3 Schedule of Assessments 25
2 Introduction 33
2.1 Trial Rationale 33
2.2 Background 34
2.3 Known and Potential Risks and Benefits 35
3 Objectives and Endpoints 38
4 Trial Design 39
4.1 Type/Design of Trial 39
4.2 Scientific Rationale for Trial Design 41
4.3 Dosing Rationale 42
4.4 Start and End-of-trial Definitions 42
4.5 Definition of Completed Subjects 43
5 Trial Population 43
5.1 Subject Selection and Numbering 43
5.2 Eligibility Criteria 44
5.2.1 Inclusion Criteria 44
5.2.2 Exclusion Criteria 45
5.3 Lifestyle Considerations 50
5.3.1 Meals and Dietary Restrictions 50
5.3.2 Caffeine, Alcohol, and Tobacco 50
5.3.3 Activity 50
5.4 Screen Failures 50
6 Trial Intervention(s) and Concomitant Therapy 51

6.1 Trial Intervention(s) Administered....51
6.1.1 Phase A - Single-blind Prospective Treatment Phase (All Subjects – Baseline to Week 8)....51
6.1.1.1 Administration of SEP-363856 With CYP2D6 Inhibitors....53
6.1.1.2 Dosing Schedules for Each Antidepressant Therapy....53
6.1.2 Phase B - Double-blind Randomization Phase (Inadequate Responders)....58
6.1.3 Phase A+ (Responders – Week 9 to 14)....60
6.1.4 Medical Devices....60
6.2 Management of Investigational Medicinal Product....60
6.2.1 Packaging and Labeling....60
6.2.2 Storage....61
6.2.3 Accountability....61
6.2.4 Returns and Destruction....61
6.2.5 Reporting of Product Quality Complaints....61
6.2.5.1 Eliciting and Reporting Product Quality Complaints....62
6.2.5.2 Information Required for Reporting Purposes....62
6.2.5.3 Return Process....62
6.2.5.4 Assessment/Evaluation....62
6.3 Measures to Minimize/Avoid Bias....63
6.4 Subject Compliance....63
6.5 Concomitant Medications or Therapies....63
6.5.1 Prohibited Medications or Therapies....64
6.5.2 Permitted Medications or Therapies....67
6.5.3 Rescue Medications....68
6.6 Intervention After the End of the Trial....68
7 Discontinuation of Trial/Treatment and Subject Discontinuation/Withdrawal....68
7.1 Entire Trial or Treatment....68
7.2 Individual Site Discontinuation....68
7.3 Discontinuation of Trial Intervention....68
7.3.1 Interruption of Trial Intervention....68
7.3.2 Rechallenge....69
7.4 Subject Discontinuation/Withdrawal From the Trial....69

7.4.1 Documenting Reasons for Subject Discontinuation/Withdrawal 70
7.4.2 Options for Continued Trial Participation 71
7.5 Lost to Follow-up 71
8 Trial Procedures 72
8.1 Efficacy Assessments 72
8.1.1 Montgomery Åsberg Depression Rating Scale 72
8.1.2 Clinical Global Impression - Severity of Illness 72

CCI

[redacted]

8.6 Safety Assessments 76
8.6.1 Clinical Laboratory Assessments 76
8.6.2 Physical Examination 77
8.6.3 Vital Signs 77
8.6.4 12-Lead Electrocardiogram 78
8.6.5 Suicidality Monitoring 78
8.6.6 Other Safety Variables 79
8.6.6.1 Extrapyramidal Symptoms 79
8.6.6.1.1 Simpson Angus Scale 79
8.6.6.1.2 Abnormal Involuntary Movement Scale 79
8.6.6.1.3 Barnes Akathisia Rating Scale 80
8.6.6.2 Sexual Function 80

8.6.6.3 Pittsburgh Sleep Quality Index 80
8.7 Adverse Events 81
8.7.1 Definitions 81
8.7.2 Eliciting and Reporting Adverse Events 83
8.7.3 Immediately Reportable Events 84
8.7.4 Medical Device Incidents (Including Malfunctions) 84
8.7.5 Adverse Events of Special Interest 84
8.7.6 Potential Serious Hepatotoxicity 84
8.7.7 Procedure for Breaking the Blind 84
8.7.8 Follow-up of Adverse Events 85
8.7.8.1 Follow-up of Nonserious Adverse Events 85
8.7.8.2 Follow-up of Immediately Reportable Events 85
8.7.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact 86
8.8 Treatment of Overdose 86
8.9 Subject Assessment Recording 86
8.10 Other Assessments 86
8.10.1 Structured Clinical Interview for *DSM-5*, Clinical Trials Version 86
8.10.2 Massachusetts General Hospital Antidepressant Treatment Response Questionnaire 87
9 Statistical Considerations 87
9.1 Sample Size 87
9.2 Datasets for Analysis 87
9.3 Handling of Missing Data 88
9.4 Statistical Analyses 88
9.4.1 Efficacy Analyses 88
9.4.1.1 Primary Efficacy Endpoint Analysis 88
9.4.1.2 Sensitivity Analyses of Primary Endpoint 91

CCI

[redacted]

9.4.1.3 Key Secondary Efficacy Endpoint Analysis 93

CCI

9.4.1.5 Control of Experiment-wise Type 1 Error 95
9.4.1.6 Phase A/A+ 95
9.4.2 Safety Analysis 95
9.4.2.1 Adverse Events 95
9.4.2.2 Clinical Laboratory Data 95
9.4.2.3 Physical Examination and Vital Signs Data 96
9.4.2.4 Electrocardiogram Data 96
9.4.2.5 Other Safety Data 96
9.4.2.5.1 Extrapyramidal Symptoms 96
9.4.2.5.2 Sexual Function 96
9.4.2.5.3 Pittsburgh Sleep Quality Index 96
9.4.2.5.4 Suicidality 97
9.4.3 Other Analyses 97
9.4.3.1 Analysis of Demographic and Baseline Characteristics 97

CCI

9.5.1 Data Monitoring Committee 98
10 Supporting Documentation and Operational Considerations 99
10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations 99
10.1.1 Ethics and Responsibility 99
10.1.2 Informed Consent 99
10.1.3 Recruitment Strategy 101
10.1.4 Confidentiality 101
10.1.5 Quality Control and Quality Assurance 101
10.1.5.1 Monitoring 101
10.1.5.2 Auditing 102
10.1.6 Protocol Deviations 102

10.1.7 Records Management 102
10.1.7.1 Source Documents 102
10.1.7.2 Data Collection 103
10.1.7.3 File Management at the Trial Site 104
10.1.7.4 Records Retention at the Trial Site 104
10.1.7.5 Dissemination of Clinical Trial Data 105
10.1.7.6 Publication Authorship Requirements 105
10.2 Appendix 2: Clinical Laboratory Tests 107
10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information 108
10.4 Appendix 4: Protocol Amendments 110

CCI

11 References 128

List of In-text Tables

Table 1.3-1	Schedule of Assessments - Screening and Phase A (All Subjects)	25
Table 1.3-2	Schedule of Assessments - Phase B (Inadequate Responders) and Phase A+ (Responders)	29
Table 3-1	Trial Objectives and Endpoints	38
Table 6.1.1.2-1	Daily Dosing Schedule for Escitalopram	54
Table 6.1.1.2-2	Daily Dosing Schedule for Fluoxetine	55
Table 6.1.1.2-3	Daily Dosing Schedule for Paroxetine ER	55
Table 6.1.1.2-4	Daily Dosing Schedule for Sertraline	56
Table 6.1.1.2-5	Daily Dosing Schedule for Duloxetine	57
Table 6.1.1.2-6	Daily Dosing Schedule for Venlafaxine XR	58
Table 6.1.2-1	Daily Dosing Scheme for SEP-363856 or Matching Placebo in Phase B	59
Table 6.5.1-1	List of Medications Prohibited Before the Trial	64
Table 6.5.1-2	List of Medications/Therapies Prohibited During the Trial	65

List of In-text Figures

Figure 1.2-1 Trial Design Schematic.....24

List of Abbreviations

Abbreviation	Definition
5-HT_{1A}	Serotonin 1A receptor
5-HT_{2A}	Serotonin 2A receptor
ADT	Antidepressant therapy
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve calculated from time zero to infinity
AxMP	Auxiliary medicinal product
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CCI	[redacted]
CGI-S	Clinical Global Impression - Severity of Illness
CIOMS	Council for International Organizations of Medical Science
C_{max}	Maximum (peak) plasma concentration of the drug
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CRO	Clinical research organization
CSFQ	Changes in Sexual Functioning Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
CYP2B6	Cytochrome P450 2B6
CYP2D6	Cytochrome P450 2D6
D_2	Dopamine 2 receptor
CCI	[redacted]
DMC	Data monitoring committee
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
eICF	Electronic informed consent form
EM	Extensive metabolizer
EPS	Extrapyramidal symptoms
ER	Extended-release
ET	Early termination
FAS	Full Analysis Set
CCI	[redacted]
GCP	Good Clinical Practice

GEE	Generalized estimating equations
CCI	[redacted]
$HAM\text{-}D_{17}$	17-item Hamilton Depression Rating Scale
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
K_2-EDTA	Dipotassium ethylenediaminetetraacetic acid
LOCF	Last observation carried forward
LOE	Lack of efficacy
LS	Least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	Missing at random
MCAR	Missing completely at random
MCMC	Monte Carlo Markov Chain
MDD	Major depressive disorder
MDE	Major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MI	Multiple imputation
CCI	[redacted]
MP	Medicinal product
MTD	Maximum tolerated dose
OC	Observed cases
OCT2	Organic Cation Transporter 2
PANSS	Positive and Negative Syndrome Scale
CCI	[redacted]
PMM	Pattern mixture models
POCBP	Persons of childbearing potential
PQC	Product quality complaint
PSQI	Pittsburgh Sleep Quality Index
PT	Prothrombin time
REM	Rapid eye movement

CCI	
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
CCI	
SIGMA	Structured Interview Guide for the MADRS
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TAAR1	Trace amine-associated 1 receptors
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WGEE	Weighted generalized estimating equations
XR	Extended-release

1 Protocol Summary

1.1 Synopsis

Name of Clinical Trial Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Product: SEP-363856

Protocol No.: 382-201-00001

IND No.: 161135

EU Trial No.: 2022-500538-27-00

Protocol Title: A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Flexible Doses of SEP-363856 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder

Protocol Lay Person Short Title: A Trial of the Safety and Efficacy of Flexible Doses of SEP-363856 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder

Clinical Phase: 2/3. This trial is not a low-interventional trial as SEP-363856 is not marketed/authorized.

Planned Treatment/Indication: Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults

Trial Rationale: To date, no clinical trials of SEP-363856 have been conducted evaluating adjunctive treatment of subjects with MDD. However, the available nonclinical as well as clinical data from other populations (sustained improvement in Montgomery Åsberg Depression Rating Scale [MADRS] total score in subjects with schizophrenia) coupled with the favorable safety and tolerability profile of SEP-363856 relative to available therapies (eg, improved metabolic profile and cardiovascular profile) support development of SEP-363856 as a potential therapy for adjunctive treatment of MDD in subjects with an inadequate response to antidepressant therapy (ADT).

Objectives and Endpoints: The trial objectives and endpoints are summarized in the table below.

Trial Objectives and Endpoints	
Objectives	**Endpoints**
Primary: • To compare the efficacy of SEP-363856 (50 to 75 mg/day) to placebo as adjunctive therapy to an assigned open-label ADT in subjects with MDD who demonstrate an inadequate response to a prospective 8-week trial of the same assigned open-label ADT.	Primary Efficacy: • Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the MADRS total score.
	Key Secondary Efficacy: • Change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in the CGI-S.
	CCI [redacted]

Trial Objectives and Endpoints	
Objectives	**Endpoints**
	CCI [redacted]
Secondary: • To evaluate the safety and tolerability of SEP-363856 (50 to 75 mg/day) as adjunctive therapy to ADT in subjects with MDD.	Safety: • Standard safety variables to be examined in this trial will include AEs, physical examinations (including body weight and waist circumference), vital signs (blood pressure, heart rate, and body temperature), 12-lead ECGs, and clinical laboratory assessments (hematology, serum chemistry, urinalysis, prolactin, glycosylated hemoglobin, and coagulation parameters). In addition to the standard safety variables, other safety variables including C-SSRS, SAS, AIMS, BARS, CSFQ, and PSQI will also be evaluated.

ADT = antidepressant therapy; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CCI [redacted] - Change; CGI-S = Clinical Global Impression - Severity of Illness; CSFQ = Changes in Sexual Functioning Questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition; ECG = electrocardiogram; CCI [redacted] ; MADRS = Montgomery Åsberg Depression Rating Scale; PSQI = Pittsburgh Sleep Quality Index; SAS = Simpson Angus Scale; CCI [redacted]

Trial Design: This is a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial designed to assess the safety and efficacy of SEP-363856 (50 to 75 mg/day) as adjunctive therapy to an assigned open-label ADT in subjects with MDD who have demonstrated an inadequate response to a prospective 8-week trial of the same assigned open-label ADT. Personnel at the site will be blinded to the randomization criteria at the end of the prospective period (ie, definition of inadequate response). The trial will be organized as follows:

Screening Period: The screening period will last up to 28 days and will begin when informed consent is signed. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to washout prohibited concomitant therapy, if applicable.

If applicable, eligible subjects will washout from their current ADT for a minimum of 24 hours before receiving the first dose of investigator-assigned ADT in Phase A. In instances where a subject will be assigned to the same ADT, the 24-hour washout period is not necessary (ie, a prior course of treatment with 1 of the protocol-specified ADTs that was at an adequate dose based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [MGH-ATRQ], but of insufficient duration [ie, < 6 weeks]).

Phase A (Single-blind Prospective Treatment Phase): Subjects meeting eligibility criteria will be enrolled into the 8-week single-blind prospective treatment phase (Phase A). CCI [redacted]

Phase B (Double-blind Randomization Phase): Subjects with an inadequate response in Phase A who are negative for tetrahydrocannabinol (THC) and illicit drugs at the Week 6 visit and who are suitable for randomization, may be randomized at the end of prospective treatment (Week 8 visit of Phase A) in a 1:1 ratio to one of the following double-blind treatment regimens:

- Continued placebo + ADT (that is, placebo plus the final dosage of the assigned open-label marketed ADT reached during Phase A), or
- SEP-363856 + ADT (that is, adjunctive SEP-363856, 50 to 75 mg/day, plus the final dosage of the assigned open-label marketed ADT reached during Phase A).

CCI [redacted]

CCI [redacted]

The dose of ADT in Phase B will be based on the final dosage of the assigned open-label ADT reached during Phase A. During Phase B, randomized subjects will attend weekly visits at Weeks 9, 10, 11, 12, 13, and 14.

Continued Treatment in Phase A+ (Single-blind Phase A responder): CCI [redacted]

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the early termination (ET) evaluations. Following the completion of all scheduled visits, subjects will be prescribed appropriate ADT (as per investigator judgment) and subjects (completers and early withdrawals) will be followed-up to monitor for safety events via telephone or a clinic visit for 7 (± 2) days after the last dose of IMP. This contact also applies to subjects withdrawn prematurely from the trial.

Trial Population: It is anticipated that approximately 900 subjects will be enrolled into Phase A (single-blind prospective treatment phase) in order to randomize approximately 310 subjects into Phase B (double-blind randomization phase).

Key Inclusion/Exclusion Criteria: The trial population will include subjects 18 to 65 years of age, inclusive, at the time of informed consent with a primary diagnosis of MDD, and in a current major depressive episode (MDE), as defined by *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria and confirmed by both the Structured Clinical Interview for *DSM-5*, Clinical Trials Version (SCID-5-CT) and an adequate clinical psychiatric evaluation. The current MDE must be ≥ 8 weeks and < 2 years in duration. Additionally, subjects must have a reported a history for the current MDE of an inadequate response to at least 1 and no more than 3 adequate ADTs. Subjects must also have a 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) total score ≥ 18 at the screening and baseline visits.

Any subject who, in the opinion of the clinical trial sponsor, investigator, or medical monitor, should not participate in the trial will be excluded.

Trial Site(s): Subjects will be enrolled from trial sites in the United States (US) and other global trial sites.

Trial Intervention(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Phase A - Single-blind Prospective Treatment Phase (All Subjects – Baseline to Week 8)

CCI



Phase B - Double-blind Randomization Phase (Inadequate Responders)

At the Week 8 visit, subjects with an inadequate response to prospective treatment with ADT (ie, meet blinded score-based criteria for inadequate response) who are otherwise eligible for randomization will be randomized into Phase B and will receive 1 of the following double-blind treatment regimens in a 1:1 ratio:

- Continued placebo + ADT (that is, placebo plus the final dosage of the assigned open-label ADT reached during Phase A), or
- SEP-363856 + ADT (50 to 75 mg/day, plus the final dosage of the assigned open-label ADT reached during Phase A).

All doses of SEP-363856 and matching placebo should be taken orally at approximately the same time each evening at bedtime and can be administered without regard to meals. The assigned ADT should be taken orally and dosed at approximately the same time each day. It is preferred that the subject take the ADT dose at the same time as the blinded IMP in the evening. Subjects must continue on the same ADT that was assigned in Phase A at the final dose taken in Phase A.

The initial dose of SEP-363856 dispensed to randomized subjects at the Week 8 visit will be 25 mg SEP-363856 (or matching placebo). The dose of SEP-363856 will then be increased to 50 mg four days after the Week 8 visit and all subjects will receive 75 mg by the Week 9 visit.

Subjects who experience dose-related tolerability issues at the 75 mg dose of SEP-363856 may decrease to 50 mg at any time after the Week 9 visit (via a scheduled or unscheduled visit).

Increases (rechallenge) in the dose of SEP-363856 (from 50 to 75 mg/day) can be made at Week 10, 11, or 12. The dose of SEP-363856 cannot be increased after the Week 12 visit. Subjects unable to tolerate the 50 mg dose of SEP-363856 (or matching placebo) will be withdrawn from the trial.

No dose adjustments to ADTs are permitted during Phase B of the trial.

Phase A+ (Responders – Week 9 to 14)

CCI [redacted]

CCI [redacted]

Trial Assessments:

Assessments for Efficacy: MADRS, Clinical Global Impression – Severity of Illness (CGI-S), CCI [redacted], CCI [redacted]

CCI [redacted]

Assessments for Safety: Adverse events (AEs), clinical laboratory assessments, physical examinations, vital signs, 12-lead electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS), Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Changes in Sexual Functioning Questionnaire (CSFQ), and Pittsburgh Sleep Quality Index (PSQI).

Screening and Other Assessments: Structured Clinical Interview for *DSM-5* (SCID-5-CT), Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ), blood alcohol test, urine drug screen, urine pregnancy test, CCI [redacted]

Independent Data Monitoring Committee: Yes, an independent data monitoring committee will be established and conduct periodic safety reviews of unblinded safety data.

Statistical Methods:

Sample Size

The sample size is calculated based on a between-group difference CCI [redacted] will yield at least 85% power to detect the treatment effects at a 2-tailed significance level of 0.05. CCI [redacted]

Primary Efficacy Endpoint Analysis

For the primary analysis of the primary endpoint, unobserved future data after participant discontinuation due to lack of efficacy and AE will be imputed using placebo-based multiple imputation under the MNAR assumption.

The null hypothesis of the statistical test comparing SEP-363856 + ADT and placebo + ADT, based on the primary efficacy endpoint, is that the change in MADRS total score using SEP-363856 + ADT is equal to the change in MADRS using the placebo + ADT.

The primary analysis will be performed on the Full Analysis Set. CCI [redacted]

Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy variable is the change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in CGI-S.

CCI [redacted]

Trial Duration:

Each subject in this trial is expected to participate in the following periods of the trial:

- *Screening Period:* Up to 28 days
- *Phase A (Single-blind Prospective Treatment Phase):* 8 weeks
- *Phase B (Double-blind Randomization Phase) or Phase A+ (Single-blind Phase A Responder):* 6 weeks
- *Follow-up:* 7 (± 2) days after the last dose of IMP

The trial start is defined as the date the first subject signs their informed consent form. Overall, the trial duration, from signing of the first subject's informed consent form to the last subject's final assessment, is expected to be approximately 36 months.

Known and Potential Risks and Benefits:

A comprehensive nonclinical safety program has been completed. Based on the nonclinical studies conducted to date, potential observations in humans following administration of SEP-363856 include signs of central nervous system (CNS) stimulation (ie, agitation, restlessness, insomnia) or depression (lethargy, somnolence, shallow breathing) depending on dose, impaired muscle coordination, effects on heart rate, and change in pupil size. These effects are readily monitorable with routine assessments in clinical trials.

Across clinical trials, SEP-363856 has been generally well-tolerated. The majority of AEs observed to date have been mild to moderate in severity and nonserious.

For the 210 healthy subjects dosed with SEP-363856 in completed single-dose, phase 1 trials, the most frequently reported AEs (≥ 5% of subjects) were somnolence (24.3%), dizziness (17.6%), nausea (15.2%), orthostatic hypotension (14.8%), dry mouth (5.7%), and headache (5.7%).

For the 657 subjects diagnosed with schizophrenia dosed with unblinded or open-label SEP-363856 in phase 1, 2, and 3 trials, the most frequently reported AEs (≥ 5% of subjects) for the pooled population were somnolence (17.5%), nausea (11.7%), headache (12.3%), dizziness (8.5%), schizophrenia (8.8%), and insomnia (7.2%). A single event of hypotension consistent with increased vagal tone, following administration of 150 mg SEP-363856, was assessed as serious.

A total of 51 serious adverse events (SAEs) were reported for subjects who received unblinded or open-label SEP-363856 in completed or ongoing trials. An additional 62 SAEs have been reported in ongoing blinded studies in subjects with schizophrenia. Most treatment-emergent SAEs were reported for subjects with schizophrenia who were enrolled in the trials and were consistent with the manifestations of the underlying disease.

Adverse events leading to IMP/trial discontinuation observed across the clinical development program have also generally been consistent with the underlying disease and/or the known safety profile of SEP-363856. CCI [redacted] The majority of AEs leading to discontinuation occurred in the schizophrenia population and there were no AEs leading to discontinuation for healthy subjects in phase 1 trials.

Two deaths have occurred in the clinical development program for SEP-363856. One death was due to acute cardiovascular insufficiency and final autopsy results identified significant chronic coronary heart disease as contributing to the cause of death. One death due to completed suicide was considered not related to SEP-363856, with the pre-existing underlying illness of schizophrenia considered a relevant confounder.

Evaluation of available accumulating safety data from the completed and ongoing SEP-363856 trials has revealed hypotension/orthostatic hypotension as an identified risk for healthy volunteers and a potential risk for subjects with schizophrenia; however, SAEs associated with hypotension/orthostatic hypotension have been reported infrequently for healthy subjects. Three events in healthy subjects assessed as serious following administration of 50 mg SEP-363856 included 1 event of hypotension which required treatment with oral fluids and oxygen and 2 events of orthostatic hypotension with persistent clinical symptoms (nausea, dizziness, pallor, and/or diaphoresis) which required treatment with intravenous normal saline. In general, treatment-emergent adverse events (TEAEs) of hypotension and orthostatic hypotension observed to date in trials of subjects with schizophrenia have been transient, mild or moderate in severity, and did not require concomitant treatment or intervention.

Drug-drug interactions with ADT treatment are often a result of cytochrome P450 (CYP) enzyme induction or inhibition. SEP-363856 is a substrate and inhibitor of CYP2D6 and an inducer of CYP2B6. Based on in vitro CYP inhibition/induction results, clinical PK data, and static mechanistic modelling of data from in vitro and in vivo studies, SEP-363856 has low potential to act as a victim or perpetrator of CYP-mediated drug-drug interactions, except as a victim of a coadministered strong CYP2D6 inhibitor. No dose adjustments based on CYP2D6 metabolizer status are necessary. Caution is recommended when SEP-363856 is coadministered with strong CYP2D6 inhibitors, and a dose reduction should be considered if adverse effects are observed. Based on in vitro transporter substrate/inhibition studies, SEP-363856 has potential to act as an inhibitor of OCT2 transporter, which is under further investigation in Study SEP361-110. There are no other unique risks anticipated in the MDD population.

Monitoring for potential AEs is incorporated into the design of this trial through safety assessments.

A direct health benefit from receipt of the SEP-363856 in subjects with MDD has not yet been established; however, data from this trial will contribute to the development of SEP-363856.

1.2 Schema

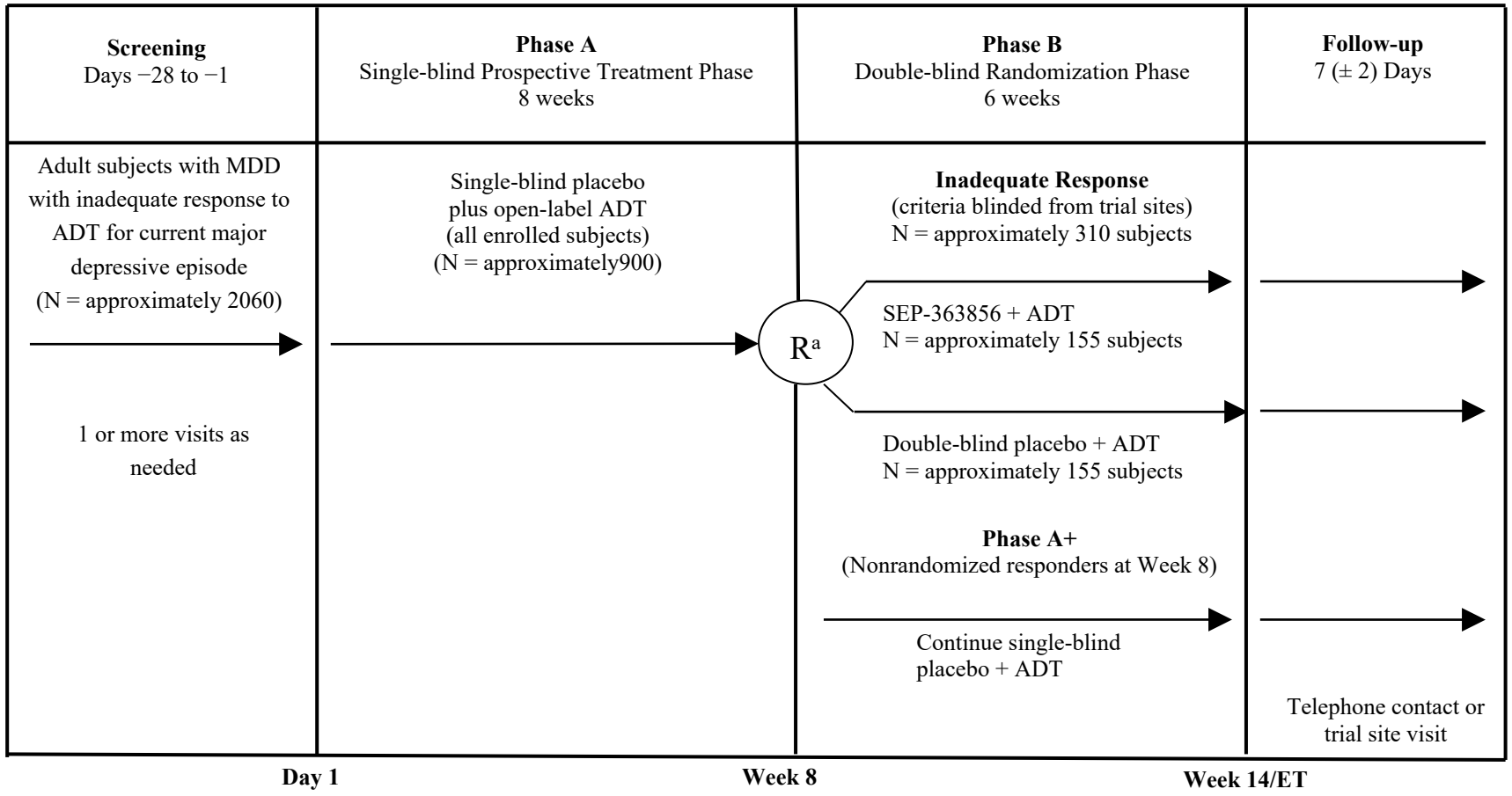


Figure 1.2-1 Trial Design Schematic

ET = early termination; ADT = antidepressant therapy; MDD = major depressive disorder.

[a]Randomization ratio of 1:1.

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments - Screening and Phase A (All Subjects)

Assessment	Visit										
	Screening Days −28 to −1	CCI								Follow-up (7 days)[b]	Notes
Visit allowance (days)	-	CCI								± 2	
ENTRANCE/HISTORY											
Informed consent	X										Section 10.1.2
Inclusion/ exclusion criteria	X	X									Section 5.2
Demography	X										
Medical history	X										
Psychiatric history	X										
SCID-5-CT	X										Section 8.10.1
Antidepressant history (MGH-ATRQ)	X										Section 8.10.2
Prior medication washout[c]	X										Section 6.5.1
EFFICACY[d]											
MADRS		X		X		X	X	X	X		Section 8.1.1
CGI-S		X	X	X	X	X	X	X	X		Section 8.1.2
CCI											

Table 1.3-1	**Schedule of Assessments - Screening and Phase A (All Subjects)**										
Assessment	**Visit**										
	Screening Days −28 to −1	CCI								**Follow-up (7 days)[b]**	**Notes**
Visit allowance (days)	**-**	CCI								**± 2**	
SAFETY											
Assess need for ADT dose modification[f]			X	X	X	X					Section 6.1.1
Physical examination[g]	X							X	X		Section 8.6.2
Vital signs[h]	X	X	X	X	X	X	X	X	X		Section 8.6.3
12-lead ECG[i]	X	X						X	X		Section 8.6.4
Clinical laboratory assessments (hematology, serum chemistry, urinalysis, and prolactin)	X	X						X	X		Section 8.6.1
Glycosylated hemoglobin	X	X						X			Section 8.6.1
TSH, with reflex to thyroxine if TSH is abnormal	X										Section 8.6.1
Coagulation parameters (PT, aPTT, INR)	X	X						X	X		Section 8.6.1
Blood alcohol[j]	X						X				Section 8.6.1
Urine drug screen[j]	X						X		X		Section 8.6.1
Urine pregnancy test (POCBP only)	X	X				X		X	X		Section 10.3
SAS								X			Section 8.6.6.1.1
AIMS								X			Section 8.6.6.1.2
BARS								X			Section 8.6.6.1.3
CSFQ		X						X	X		Section 8.6.6.2

Table 1.3-1 Schedule of Assessments - Screening and Phase A (All Subjects)

Assessment	Visit										
	Screening Days −28 to −1	CCI								Follow-up (7 days)[b]	Notes
Visit allowance (days)	-	-	± 2	± 2	± 2	± 2	± 2	± 2	-	± 2	
PSQI		X						X	X		Section 8.6.6.3
C-SSRS[k]	X	X	X	X	X	X	X	X	X		Section 8.6.5
Adverse events	X	X	X	X	X	X	X	X	X	X	Section 8.7
Concomitant medications	X	X	X	X	X	X	X	X	X	X	Section 6.5
OTHER											
CCI											
Blinded IMP and ADT dispensing		X	X	X	X	X	X	X[n,o]			
Blinded IMP and ADT accountability			X	X	X	X	X	X			

aPTT = activated partial thromboplastin time; ET = early termination; ICF = informed consent form; INR = international normalized ratio; CCI PT = prothrombin time; TSH = thyroid stimulating hormone.

[a]If a subject discontinues prematurely before Week 8, every effort should be made to complete the ET evaluations.

[b]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety for subjects that discontinue prematurely before Week 8.

[c]Washout of prohibited medications begins after signing the ICF and must comply with the required washout periods. CCI

[d]Efficacy assessments should be completed prior to safety assessments and CCI

[e]The trial site will be notified of the subject's response status CCI [redacted]

[f]The investigator will increase the dose of ADT to the maximum effective dose by Week 3. No dose increases in ADT are permitted after the Week 3 visit. No dose decreases are permitted after the Week 4 visit. Any subject not able to tolerate a therapeutic dose of ADT must be withdrawn from the trial.

[g]Height, body weight, and waist circumference will be measured at screening. Body weight and waist circumference will be measured at all other time points.

[h]Vital signs include blood pressure, heart rate, and body temperature. Blood pressure and heart rate measurements will be taken in a supine and standing position. Blood pressure and heart rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. Vital signs scheduled at the same visit as blood samples are to be completed before blood is drawn.

[i]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes. Subjects will continue in the trial based on Week 8 ECG results from the trial site. The ECGs scheduled for the same visit as blood sample collections are to be completed before blood is drawn.

[j]Eligibility for continuation in the trial beyond the Week 8 visit is based in part on the Week 6 urine drug screen and blood alcohol results. A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator. Subjects testing positive for THC at the screening visit must agree to abstain from use of cannabis products for the duration of the trial and must test negative for THC prior to the completion of the screening period. These subjects must also test negative for THC at the baseline visit prior to enrollment.

[k]The "Baseline/Screening" C-SSRS form will be completed for all subjects at screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the baseline visit to assure that the subject continues to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at CCI [redacted]

CCI [redacted]

[n]No change in the ADT (ie, drug or dose) is permitted for subjects entering Phase B at Week 8. CCI [redacted]

[o]IMP and ADT dispensation at Week 8 to occur after Week 8 eligibility assessments are completed and it is determined whether the subject will continue in either Phase A+ or Phase B.

Table 1.3-2 Schedule of Assessments - Phase B (Inadequate Responders) and Phase A+ (Responders)											
	Phase B Visit (Double-blind Randomization Phase)[a]							Phase A+ Visit (Further Single-blind Treatment for Week 8 Responders)[b]		Follow-up (7 days)[d]	Notes
Assessment	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Week 13**	**Week 14 /ET[c]**	CCI			
Visit allowance (days)	**(Phase B Baseline)**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
EFFICACY[e]											
MADRS	CCI	X	X	X	X	X	X		X	X	Section 8.1.1
CGI-S	CCI	X	X	X	X	X	X		X	X	Section 8.1.2
CCI											
SAFETY											
Physical examination[h]							X		X		Section 8.6.2
Vital signs[i]		X	X	X	X	X	X	X	X		Section 8.6.3
12-lead ECG[j]		X	X				X		X		Section 8.6.4
Clinical laboratory tests (hematology,			X				X		X		Section 8.6.1

Table 1.3-2 Schedule of Assessments - Phase B (Inadequate Responders) and Phase A+ (Responders)											
	Phase B Visit (Double-blind Randomization Phase)[a]							Phase A+ Visit (Further Single-blind Treatment for Week 8 Responders)[b]		Follow-up (7 days)[d]	Notes
Assessment	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Week 13**	**Week 14 /ET[c]**	CCI			
Visit allowance (days)	**(Phase B Baseline)**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
serum chemistry, urinalysis, and prolactin)											
Glycosylated hemoglobin							X				Section 8.6.1
Coagulation parameters (PT, aPTT, INR)			X				X		X		Section 8.6.1
Urine pregnancy test (POCBP only)					X		X	X	X		Section 8.6.1
SAS		X			X		X		X		Section 8.6.6.1.1
AIMS		X			X		X		X		Section 8.6.6.1.2
BARS		X			X		X		X		Section 8.6.6.1.3
CSFQ							X		X		Section 8.6.6.2
C-SSRS		X	X	X	X	X	X	X	X	X	Section 8.6.5
PSQI							X		X		Section 8.6.6.3
Adverse events		X	X	X	X	X	X	X	X	X	Section 8.7
Concomitant medications		X	X	X	X	X	X	X	X	X	Section 6.5

Table 1.3-2 Schedule of Assessments - Phase B (Inadequate Responders) and Phase A+ (Responders)											
	Phase B Visit (Double-blind Randomization Phase)[a]							Phase A+ Visit (Further Single-blind Treatment for Week 8 Responders)[b]		Follow-up (7 days)[d]	Notes
Assessment	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Week 13**	**Week 14 /ET[c]**	CCI			
Visit allowance (days)	**(Phase B Baseline)**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
OTHER											
CCI											
Blinded IMP and ADT dispensing		X	X	X	X	X		X			
Blinded IMP and ADT accountability		X	X	X	X	X	X	X	X		
Urine drug screen[m]							X		X		Section 8.6.1

CCI [redacted]

CCI [redacted]

[c]If a subject discontinues prematurely, procedures noted for Week 14 must be completed at the ET visit according to the trial phase from which the subject withdrew. CCI [redacted]

[d]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety.

CCI [redacted]

CCI [redacted]

[h]Includes body weight and waist circumference.

[i]Vital signs include blood pressure, heart rate, and body temperature. Blood pressure and heart rate measurements will be taken in a supine and standing position. Blood pressure and heart rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. Vital signs scheduled at the same visit as blood samples are to be completed before blood is drawn.

[j]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. The ECGs scheduled for the same visit as blood sample collections are to be completed before blood is drawn.

CCI [redacted]

CCI [redacted] CCI [redacted] CCI [redacted]

[m]Only required for subjects who discontinue prematurely from the trial and attend an ET visit.

2 Introduction

SEP-363856 is a new molecular entity being developed by Otsuka Pharmaceutical Development & Commercialization, Inc./Otsuka Pharmaceutical Co. Ltd. (Otsuka).

This is a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial designed to assess the safety and efficacy of SEP-363856 as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in subjects with major depressive disorder (MDD) who have demonstrated an inadequate response to an 8-week prospective trial of the same ADT.

2.1 Trial Rationale

SEP-363856 is a novel central nervous system (CNS)-active compound, which shows broad efficacy in animal models of schizophrenia (positive and negative symptoms), anxiety, and depression.

Nonclinical models of antidepressant activity support clinical trials of SEP-363856 in patients with MDD. In rodent nonclinical models, SEP-363856 showed antidepressant- and anxiolytic-like effects following acute, sub-chronic, and chronic dosing. Functional imaging and electrophysiology studies in rodents showed that SEP-363856 modulates neural activity in several highly interconnected brain regions, including limbic and monoaminergic nuclei, that regulate mood, anxiety, reward processing, and cognition. SEP-363856 modestly increased extracellular levels of norepinephrine and acetylcholine in the rat prefrontal cortex and/or hippocampus, without producing effects on dopamine and serotonin release, indicating differentiation from standard antidepressants (eg, selective serotonin reuptake inhibitors). SEP-363856 reduced rapid eye movement (REM) sleep in rats, a translatable pharmacodynamic effect exhibited by most antidepressant drugs. The REM sleep-suppressing effects of SEP-363856 were translated to humans in a dedicated phase 1 clinical trial in healthy male subjects (SEP361-103).[1]

The mechanism of action of SEP-363856 has not been fully elucidated; however, data from nonclinical studies suggest that agonism at trace amine-associated 1 receptors (TAAR1) and serotonin 1A receptors (5-HT_{1A}) contributes to its efficacy. Antidepressant-like and anxiolytic-like effects have been reported for TAAR1 and 5-HT_{1A} agonists in nonclinical models and/or clinical studies.[2,3] SEP-363856 did not exhibit meaningful activity and/or receptor occupancy at the primary targets for antidepressant drugs (eg, serotonin transporter, norepinephrine transporter, dopamine transporter, monoamine oxidase A and B, or agents used to augment treatment response

in MDD such as atypical antipsychotics (ie, dopamine 2 receptor [D_2] and serotonin 2A receptors [5-HT_{2A}]).

In phase 2 clinical trials in subjects with schizophrenia, SEP-363856 has demonstrated the potential for improvement of a broad range of schizophrenia symptoms, including mood and anxiety related symptoms. SEP361-201 was a 4-week, randomized, double-blind, placebo-controlled, multicenter trial evaluating the efficacy and safety of SEP-363856 (flexibly-dosed at 50 to 75 mg/day) in acutely psychotic adults with schizophrenia. SEP-363856 demonstrated statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) total score compared with placebo at Week 4 (primary endpoint), as well as all secondary efficacy endpoints, including the Montgomery-Åsberg Depression Rating Scale (MADRS). In a long-term, open-label extension trial (SEP361-202), sustained improvements were noted on efficacy measures including the MADRS for up to 26 weeks.

To date, no clinical trials of SEP-363856 have been conducted evaluating adjunctive treatment of subjects with MDD. However, the available nonclinical as well as clinical data from other populations (sustained improvement in MADRS total score in subjects with schizophrenia) coupled with the favorable safety and tolerability profile of SEP-363856 relative to available therapies (eg, improved metabolic profile and cardiovascular profile) support development of SEP-363856 as a potential therapy for adjunctive treatment of MDD in subjects with an inadequate response to ADT.

2.2 Background

A 2017 World Health Organization publication Depression and Other Common Mental Disorders: Global Health Estimates reported 322 million people across the globe, 4.4% of the world's population, are living with depression.[4] In a large 2018 United States (US) national survey, prevalence estimates for *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) MDD were even higher with 12-month and lifetime prevalence of MDD reported at 10.4% and 20.6%, respectively, with most having moderate (6 - 7 symptoms) or severe (8 - 9 symptoms) MDD that was associated with comorbidity and impairment.[5]

Major depressive disorder has a severe impact on overall functioning[6] and is a leading cause of disability worldwide in terms of total years lost due to disability.[7] Based on data from 2010, depression-related expenditures in the US were greater than $210 billion, with employers incurring $102 billion in losses due to absenteeism, presenteeism, and disability, and direct medical costs of $99 billion.[8]

Despite the availability of numerous treatments (eg, pharmacotherapy, psychotherapy, electroconvulsive therapy [ECT]), achievement of consistent and favorable long-term outcomes still represents a significant unmet medical need.[9] For patients who experience an initial major depressive episode (MDE), the probability of experiencing another episode at some point in the future can be as high as 85%.[10,11] In addition, 15% of patients may endure chronic symptoms after the first episode, while 35% may experience recurrent episodes.[12] Many patients with MDD fail to achieve an adequate treatment response. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, approximately 30% of patients achieved remission and less than 50% achieved a response with the initial ADT (citalopram).[13]

Inadequate response to treatment for MDD is associated with an increased risk of relapse[14,15] impaired social and occupational functioning[16] and consequently, an increased economic burden.[8,17,18] Practice guidelines emphasize the importance of adequate treatment for MDD, including continuation of pharmacotherapy after an initial response is achieved to prevent relapse and maintenance treatment in individuals at risk of recurrence.[19,20,21]

In patients who do not achieve an adequate response to first line treatments for MDD, a number of pharmacotherapeutic strategies are employed including switching to another agent in the same or different class, combination therapy with multiple antidepressant agents, and augmentation of ongoing antidepressant monotherapy with adjunctive atypical antipsychotic agents.[22] Atypical antipsychotics, while commonly used as adjunctive therapy, can carry varying degrees of cardiometabolic and other side effects that limit tolerability in the MDD population. Atypical antipsychotics used in adjunctive treatment of MDD also share a common antagonist activity at D_2 receptors, and therefore carry risk of inducing extrapyramidal effects. For these reasons, there exists a substantial unmet need for adjunctive agents for the treatment of MDD that alleviate residual symptoms and improve response and remission rates and are not burdened with the side effect profile associated with atypical antipsychotics.

2.3 Known and Potential Risks and Benefits

A comprehensive nonclinical safety program comprised of repeat-dose toxicology in adult and juvenile animals, in vitro and in vivo genotoxicity, carcinogenicity, reproductive and developmental toxicity, in vitro phototoxicity, and local tolerance testing has been completed. Based on the nonclinical studies conducted to date, potential observations in humans following administration of SEP-363856 include signs of CNS

stimulation (ie, agitation, restlessness, insomnia) or CNS depression (lethargy, somnolence, shallow breathing) depending on dose, impaired muscle coordination, effects on heart rate, and change in pupil size. These effects are readily monitorable with routine assessments in clinical trials.

Across clinical trials, SEP-363856 has been generally well-tolerated. The majority of AEs observed to date have been mild to moderate in severity and nonserious. Events reported as of the data cut-off date of 24 Sep 2021 are described below.

For the 210 healthy subjects dosed with SEP-363856 in completed single-dose, phase 1 trials, the most frequently reported adverse events (AEs) (≥ 5% of subjects) were somnolence (24.3%), dizziness (17.6%), nausea (15.2%), orthostatic hypotension (14.8%), dry mouth (5.7%), and headache (5.7%).

For the 657 subjects diagnosed with schizophrenia dosed with unblinded or open-label SEP-363856 in phase 1, 2, and 3 trials, the most frequently reported AEs (≥ 5% of subjects) for the pooled population were somnolence (17.5%), nausea (11.7%), headache (12.3%), dizziness (8.5%), schizophrenia (8.8%), and insomnia (7.2%). A single event of hypotension consistent with increased vagal tone, following administration of 150 mg SEP-363856, was assessed as serious.

A total of 51 serious adverse events (SAEs) were reported for subjects who received unblinded or open-label SEP-363856 in completed or ongoing trials. An additional 62 SAEs have been reported in ongoing blinded studies in subjects with schizophrenia. Most treatment-emergent SAEs were reported for subjects with schizophrenia who were enrolled in the trials and were consistent with the manifestations of the underlying disease.

Adverse events leading to investigational medicinal product (IMP)/trial discontinuation observed across the clinical development program have also generally been consistent with the underlying disease and/or the known safety profile of SEP-363856. CCI [redacted] The majority of AEs leading to discontinuation occurred in the schizophrenia population and there were no AEs leading to discontinuation for healthy subjects in phase 1 trials.

Two deaths have occurred in the clinical development program for SEP-363856. One death due to acute cardiovascular insufficiency was reported in the SEP-363856 group in Trial SEP361-201; final autopsy results identified significant chronic coronary heart disease as contributing to the cause of death. One death due to completed suicide in

Trial SEP361-303 was considered not related to SEP-363856, with the pre-existing underlying illness of schizophrenia considered a relevant confounder.

Evaluation of available accumulating safety data from the completed and ongoing SEP-363856 trials has revealed hypotension/orthostatic hypotension as an identified risk for healthy volunteers and a potential risk for subjects with schizophrenia; however, SAEs associated with hypotension/orthostatic hypotension have been reported infrequently for healthy subjects. Three events in healthy subjects assessed as serious following administration of 50 mg SEP-363856 included 1 event of hypotension which required treatment with oral fluids and oxygen and 2 events of orthostatic hypotension with persistent clinical symptoms (nausea, dizziness, pallor, and/or diaphoresis) which required treatment with intravenous normal saline. In general, treatment-emergent adverse events (TEAEs) of hypotension and orthostatic hypotension observed to date in trials of subjects with schizophrenia have been transient, mild or moderate in severity, and did not require concomitant treatment or intervention.

Drug-drug interactions with ADT treatment are often a result of cytochrome P450 (CYP) enzyme induction or inhibition. SEP-363856 is a substrate and inhibitor of CYP2D6 and an inducer of CYP2B6. Based on in vitro CYP inhibition/induction results, clinical PK data, and static mechanistic modelling of data from in vitro and in vivo studies, SEP-363856 has low potential to act as a victim or perpetrator of CYP-mediated drug-drug interactions, except as a victim of a coadministered strong CYP2D6 inhibitor. No dose adjustments based on CYP2D6 metabolizer status are necessary. Caution is recommended when SEP-363856 is coadministered with strong CYP2D6 inhibitors, and a dose reduction should be considered if adverse effects are observed. Based on in vitro transporter substrate/inhibition studies, SEP-363856 has potential to act as an inhibitor of Organic Cation Transporter 2 (OCT2) transporter, which is under further investigation in Study SEP361-110. There are no other unique risks anticipated in the MDD population.

Monitoring for potential AEs is incorporated into the design of this trial through safety assessments.

A direct health benefit from receipt of the SEP-363856 in subjects with MDD has not yet been established; however, data from this trial will contribute to the development of SEP-363856.

Please refer to the SEP-363856 Investigator's Brochure (IB)[23] and IB Addendum for MDD[24] for more detailed information. Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

3 Objectives and Endpoints

The trial objectives and endpoints are summarized in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: • To compare the efficacy of SEP-363856 (50 to 75 mg/day) to placebo as adjunctive therapy to an assigned open-label ADT in subjects with MDD who demonstrate an inadequate response to a prospective 8-week trial of the same assigned open-label ADT.	Primary Efficacy: • Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the MADRS total score.
	Key Secondary Efficacy: • Change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in the CGI-S.
	CCI [redacted]

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Secondary: • To evaluate the safety and tolerability of SEP-363856 (50 to 75 mg/day) as adjunctive therapy to ADT in subjects with MDD.	Safety: • Standard safety variables to be examined in this trial will include AEs, physical examinations (including body weight and waist circumference), vital signs (blood pressure, heart rate, and body temperature), 12-lead ECGs, and clinical laboratory assessments (hematology, serum chemistry, urinalysis, prolactin, glycosylated hemoglobin, and coagulation parameters). In addition to the standard safety variables, other safety variables including C-SSRS, SAS, AIMS, BARS, CSFQ, and PSQI will also be evaluated.

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CCI CGI-S = Clinical Global Impression - Severity of Illness; CSFQ = Changes in Sexual Functioning Questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; CCI ; CCI CCI PSQI = Pittsburgh Sleep Quality Index; SAS = Simpson Angus Scale; CCI

Section 9.4 describes the statistical analysis of the endpoints for the primary and key secondary efficacy endpoints. The estimands for primary and key secondary efficacy endpoints will be provided in the statistical analysis plan (SAP).

4 Trial Design

4.1 Type/Design of Trial

This is a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial designed to assess the safety and efficacy of SEP-363856 (50 to 75 mg/day) as adjunctive therapy to an assigned open-label ADT in subjects with MDD who have demonstrated an inadequate response to a prospective 8-week trial of the same assigned open-label ADT. Personnel at the site will be blinded to the randomization criteria at the end of the prospective period (ie, definition of inadequate response). It is anticipated that approximately 900 subjects will be enrolled into Phase A (single-blind prospective treatment phase) from trial sites in the US and other global trial sites in order to randomize approximately 310 subjects into Phase B (double-blind randomization phase).

The trial will be organized as follows:

Screening Period: The screening period will last up to 28 days and will begin when informed consent is signed. The purpose of the screening period is to assess eligibility criteria (see Section 5.2) at 1 or more visits (as necessary to complete screening assessments) and to washout prohibited concomitant therapy, if applicable.

If applicable, eligible subjects will washout from their current ADT for a minimum of 24 hours before receiving the first dose of investigator-assigned ADT in Phase A. In instances where a subject will be assigned to the same ADT, the 24-hour washout period is not necessary (ie, a prior course of treatment with 1 of the protocol-specified ADTs that was at an adequate dose based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [MGH-ATRQ], but of insufficient duration [ie, < 6 weeks]).

Phase A (Single-blind Prospective Treatment Phase): Subjects meeting eligibility criteria will be enrolled into the 8-week single-blind prospective treatment phase (Phase A).

CCI [redacted]

Phase B (Double-blind Randomization Phase): Subjects with an inadequate response in Phase A who are negative for tetrahydrocannabinol (THC) and illicit drugs at the Week 6 visit and who are suitable for randomization, may be randomized at the end of prospective treatment (Week 8 visit of Phase A) in a 1:1 ratio to one of the following double-blind treatment regimens:

- Continued placebo + ADT (that is, placebo plus the final dosage of the assigned open-label marketed ADT reached during Phase A), or
- SEP-363856 + ADT (that is, adjunctive SEP-363856, 50 to 75 mg/day, plus the final dosage of the assigned open-label marketed ADT reached during Phase A).

CCI [redacted]

CCI [redacted]

The dose of ADT in Phase B will be based on the final dosage of the assigned open-label ADT reached during Phase A. During Phase B, randomized subjects will attend weekly visits at Weeks 9, 10, 11, 12, 13, and 14.

Continued Treatment in Phase A+ (Single-blind Phase A Responder): CCI [redacted]

Follow-up: If any subject discontinues the trial early, every effort should be made to complete the early termination (ET) evaluations. Following the completion of all scheduled visits, subjects will be prescribed appropriate ADT (as per investigator judgment) and subjects (completers and early withdrawals) will be followed-up to monitor for safety events via telephone or a clinic visit for 7 (± 2) days after the last dose of IMP. This contact also applies to subjects withdrawn prematurely from the trial.

4.2 Scientific Rationale for Trial Design

This is a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial designed to assess the safety and efficacy of SEP-363856 as adjunctive therapy to an assigned open-label ADT in subjects with MDD who have demonstrated an inadequate response to an 8-week prospective trial of the same ADT. SEP-363856 has potential efficacy in MDD based on its purported mechanism of action, available nonclinical data, and clinical data from subjects with schizophrenia and improvements in the MADRS; therefore, this trial is designed to explore its efficacy as adjunctive therapy to ADT.

4.3 Dosing Rationale

In this trial, subjects randomized into Phase B will receive SEP-363856 (50 to 75 mg/day) or placebo for 6 weeks. Titration is included to improve tolerability.

Selection of these doses was guided by the results from the development program to date, including the maximum tolerated dose (MTD) from trials in subjects with schizophrenia and healthy subjects. The MTD determined for single doses of SEP-363856 administered to subjects with schizophrenia in Trial SEP361-105 was 100 mg and in healthy adult subjects in Trials SEP361-103 and SEP361-104 was 50 mg. Trial SEP361-201 demonstrated a statistically significant difference in change from baseline to Week 4 in MADRS total score for SEP-363856 (50 to 75 mg/day flexible dose) versus placebo indicating an effect on depression symptoms in adults with an acute exacerbation of schizophrenia. Trial SEP361-202 demonstrated sustained improvement in symptoms (including reductions in MADRS total score) over 26 weeks with a favorable safety and tolerability profile.

While SEP-363856 is believed to have a unique mechanism of action, nonclinical and clinical data available to date including the safety and tolerability profile of SEP-363856 relative to that of atypical antipsychotics support the characterization of the efficacy and safety of SEP-363856 50 to 75 mg/day in this phase 2/3 trial.

Details regarding the metabolization of SEP-363856 through CYP2D6 and the relevance regarding dosing in MDD are provided in Section 6.1.1.1.

4.4 Start and End-of-trial Definitions

The trial start is defined as the first visit of the first subject, which is the date the first subject signs their informed consent form.

The end-of-trial date is defined as the last date of contact, or the date of final contact attempt as recorded on the post-treatment follow-up eSource form for the last subject completing or withdrawing from the trial.

Start of recruitment is defined as the first subject first visit and end of recruitment is defined as when the clinical trial sponsor notifies trial sites that enrollment is closed.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumes all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Week 14 visit will be defined as trial completers. Protocol-specified post-treatment follow-up contacts will not qualify as the "last scheduled visit".

5 Trial Population

Approximately 900 subjects will be enrolled in Phase A and approximately 310 subjects will be randomized in Phase B. The trial population will include male and female outpatients aged 18 to 65 years with a primary *DSM-5* diagnosis of MDD and in a current MDE, with reported inadequate response (< 50% improvement in symptom severity per MGH-ATRQ) to at least 1 but no more than 3 ADTs in the current episode.

External quality oversight methods will be used by the clinical research organization (CRO) to perform an Eligibility Review process to promote appropriate subject enrollment and randomization. Subjects cannot be enrolled until the CRO eligibility review process has been completed and the site has received the final notification from the medical monitor or clinical scientist. Decisions regarding inclusion of subjects at time of enrollment and assessment of subject safety throughout the trial primarily remain at the discretion of the investigator; however, the medical monitor may recommend exclusion or discontinuation of a subject based on individual subject data.

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent [or assent if applicable]). The site number will be designated by the clinical trial sponsor.

Demographic information (collection date, date of birth, sex at birth, childbearing potential, race, ethnicity, country) and medical history will be recorded in eSource at the screening visit. Attempts should be made to obtain relevant medical and pharmacy records for subjects during screening. This is strongly encouraged to confirm past diagnoses and treatment history.

Eligible subjects who are enrolled in the trial will be assigned a unique subject randomization number for treatment sequence assignment. Results of the eligibility assessment, date of randomization (or date of treatment assignment), and randomization number (or treatment group) will be recorded in eSource.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria when assessed:

1) Subjects who are able to provide written informed consent prior to the initiation of any protocol-required procedures.
2) Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet/capsule ingestion, and discontinuation of prohibited concomitant medication; to read and understand the written word in order to complete subject-reported outcomes measures; and to be reliably rated on assessment scales.
3) Subjects 18 to 65 years of age, inclusive, at the time of informed consent.
4) Subject's body mass index (BMI) must be 18.0 kg/m^2 to 40.0 kg/m^2, inclusive, at the time screening. For subjects who are severely obese, as confirmed by a corresponding high BMI (> 35 kg/m^2), eligibility must be discussed with the medical monitor.
5) Subjects with a primary diagnosis of MDD, and in a current MDE, as defined by *DSM-5* criteria and confirmed by both the Structured Clinical Interview for *DSM-5*, Clinical Trials Version (SCID-5-CT) and an adequate clinical psychiatric evaluation. The current MDE must be ≥ 8 weeks in duration.
6) Subjects must have reported a history for the current MDE of an inadequate response to at least 1 and no more than 3 adequate ADTs. An inadequate response is defined as < 50% reduction in depressive symptom severity, as assessed by the MGH-ATRQ. Adequate treatment is defined as an ADT for at least 6 weeks in duration at a minimum therapeutic dose (or higher) as specified in the MGH-ATRQ. If the subject showed ≥ 50% improvement on any ADT in the current episode, then the subject must have had an inadequate response to a subsequent adequate ADT (as defined above by the MGH-ATRQ) of another antidepressant drug prior to entry into the trial. For the most recent antidepressant treatment, the subject must not report ≥ 50% improvement (as defined above by the MGH-ATRQ).
7) Subjects with a 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) total score ≥ 18 at the screening and baseline visits.

8) Subjects willing to discontinue all prohibited psychotropic medications to meet protocol-required washouts prior to and during the trial period.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria when assessed:

1) Sexually active subjects or persons of childbearing potential (POCBP) who do not agree to practice 2 different clinical trial sponsor approved methods of birth control or remain abstinent during the course of the trial and for 30 days after the last dose of IMP (females at birth) or 90 days after the last dose of IMP (males at birth). Unless the subject is sterile (ie, subjects who have had a bilateral oophorectomy or hysterectomy or who have not had a menstrual period for at least 12 consecutive months; or subjects who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control injection, birth control implant, birth control patch, condom with spermicide, or sponge with spermicide. Subjects who do not agree to refrain from donating sperm from screening through 90 days after the last dose of IMP. Subjects with exclusively same-sex partners may not be required to practice birth control methods following discussion with the investigator and medical monitor.
2) Subjects who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3) Subjects who report an inadequate response (less than 50% reduction in depressive symptom severity) to more than 3 monotherapy ADTs during the current MDE at a therapeutic dose (as defined by the MGH-ATRQ) and for an adequate duration (minimum duration of 6 weeks), including any antidepressant that the subject may be taking at screening if it meets the criteria for adequate treatment.
4) Subjects in a current MDE $\geq$ 2 years in duration.
5) Subjects who report treatment with oral adjunctive antipsychotic medication with an antidepressant for $\geq$ 3 weeks during the current MDE.
6) Subjects who report allergies or an intolerability (lifetime treatment history) to all trial-provided ADTs that have not been prescribed to the subject during the current major depressive episode (ie, subjects will not be assigned an ADT with which they have reported difficulties tolerating historically).
7) Subjects who have received ECT for the current MDE or within 1 year of the screening visit, whichever is longer.
8) Subjects who have had an inadequate response to ECT at any time in the past or who have had a vagus nerve stimulation or deep brain stimulation device implanted at any time for the management of treatment-resistant depression. Subjects who have had neuromodulation treatment such as transcranial magnetic stimulation during the current MDE are also excluded.

9) Subjects with a current need for involuntary commitment or who have been hospitalized within 4 weeks of screening for the current MDE.
10) Subjects with a lifetime history of meeting DSM-5 criteria for:
    - Schizophrenia spectrum or other psychotic disorder
    - Bipolar or related disorder
    - Major or mild neurocognitive disorder
    - Neurodevelopmental disorder of greater than mild severity or of a severity that impacts the participant's ability to consent, follow study directions, or otherwise safely participate in the study
    - Borderline or antisocial personality disorder

    Subjects meeting current DSM-5 criteria for:

    - Post-traumatic stress disorder
    - Obsessive compulsive disorder
    - Panic disorder
    - Eating disorder (including anorexia nervosa or bulimia)
11) Subjects experiencing hallucinations, delusions, or any psychotic symptomatology in the current MDE.
12) Subjects receiving new onset psychotherapy (individual, group, marriage, or family therapy) within 90 days of screening or at any time during participation in the trial. Ongoing psychotherapy may be permitted provided there are no changes to frequency/type expected during the trial.
13) Subjects who:
    - Answer "Yes" on the Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) within the last 6 months prior to screening or the baseline visit, OR
    - Answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) within the last 6 months prior to screening or at the baseline visit, OR
    - Answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) within 2 years prior to screening or at the baseline visit, OR
    - In the opinion of the investigator, present a serious risk of suicide.
14) Subjects who have met *DSM-5* criteria for substance use disorder within the past 12 months; including alcohol and benzodiazepines, but excluding nicotine.
15) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) and/or an abnormal result for free thyroxine at screening.

16) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, or known human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.
17) Subject has a history of a condition or previous gastrointestinal surgery (eg, cholecystectomy within 6 months of screening, vagotomy, or bowel resection) that may interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH. Subject has a history of malabsorption.
18) Subjects with Type I diabetes mellitus are excluded.

    For subjects who do not have diabetes, screening glucose must be ≤ 125 mg/dL / 6.9 mmol/L (fasting) or ≤ 179 mg/dL / 9.9 mmol/L (nonfasting); if nonfasting screening glucose is greater than this value, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL / 6.9 mmol/L.

    Subjects with Type 2 diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following:

    - Screening glucose must be ≤ 179 mg/dL / 9.9 mmol/L (fasting) or < 200 mg/dL / 11.1 mmol/L (nonfasting). If nonfasting screening glucose is ≥ 200 mg/dL / 11.1 mmol/L, subjects must be retested in a fasted state and the retest value must be ≤ 179 mg/dL / 9.9 mmol/L, AND
    - Glycosylated hemoglobin < 8.0%, AND
    - For subjects taking oral or non-insulin injectable anti-diabetic medication(s), subject has been maintained on a stable regimen of oral or non-insulin injectable anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, AND
    - Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND
    - Subject's diabetes is not newly diagnosed during screening for the trial.
    - Subjects with insulin-dependent type 2 diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the conditions above, and they have been maintained on a stable daily regimen of insulin for at least 60 days prior to screening.

19) Subjects with uncontrolled hypertension (diastolic blood pressure > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 20 mmHg in systolic blood pressure and/or a decrease of ≥ 10 mmHg in diastolic blood pressure after at least 2 to 4 minutes standing compared to the previous supine blood pressure, OR the development of symptoms (eg, dizziness) when going from supine to standing (in addition to measurements noted). NOTE: Blood pressure measurements may be repeated once at screening and once at baseline to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above. Any subject with a known cardiovascular disease or condition, including hypertension, (even if under control and considered stable) must be discussed with the medical monitor before being enrolled in the trial.
20) Subjects with known ischemic heart disease or history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery.
21) Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance, childhood febrile seizure, post-traumatic, or alcohol withdrawal.
22) Subjects with a positive urine drug screen for illicit drugs other than cannabis are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of cannabis, prescription, or over-the counter medications or products, and/or a positive blood alcohol result that in the investigator's documented opinion does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, may continue evaluation for the trial following consultation and approval by the medical monitor.

    Note that subjects testing positive for THC at the screening visit must agree to abstain from use of cannabis products for the duration of the trial and must test negative for THC prior to the completion of the screening period. These subjects must also test negative for THC at the baseline visit prior to enrollment. Additionally, subjects who test positive for THC at Week 6 will not be permitted to enter Phase B of the trial.
23) The following clinical laboratory test and electrocardiogram (ECG) results are exclusionary:
    - Platelets ≤ 75,000/mm^3
    - Hemoglobin ≤ 9 g/dL
    - Neutrophils, absolute ≤ 1000/mm^3
    - Aspartate transaminase > 2 × upper limit of normal (ULN)
    - Alanine transaminase > 2 × ULN
    - Creatine phosphokinase ≥ 3 × ULN, unless discussed with and approved by the medical monitor
    - Creatinine ≥ 2 mg/dL

- Glycosylated hemoglobin ≥ 7.0% (please refer to Exclusion Criterion #18 for subjects with Type 2 diabetes)
- Abnormal free thyroxine (Note: Free thyroxine is measured only if result for thyroid stimulating hormone is abnormal.)
- Heart rate > 100 beats per minute or < 50 beats per minute, QRS > 120 msec, QT interval as corrected for heart rate by Fridericia's formula ≥ 450 msec (males) and ≥ 470 msec (females)
- Prolactin concentration > 100 ng/mL at screening

NOTE: In addition, subjects should be excluded if they have any other abnormal clinical laboratory tests, vital sign results, or ECG findings which in the investigator's judgment are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.

24) Recent treatment with a prohibited therapy.
25) Subjects who would be likely to require prohibited concomitant therapy during the trial.
26) Subjects who received SEP-363856 in any prior clinical trial or with known hypersensitivity to any components of SEP-363856.
27) Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome.
28) Subjects with a history of true allergic response or hypersensitivity (ie, not intolerance) to more than one class of medications. Subjects with hypersensitivity to any components of the trial-assigned IMP.
29) Prisoners or subjects who are compulsorily detained (involuntarily hospitalized) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
30) Subjects who participated in a clinical trial involving an investigational drug or device within the last 90 days or who participated in more than 2 clinical trials involving an investigational drug or device within the past year.
31) Any subject who, in the opinion of the clinical trial sponsor, investigator, or medical monitor, should not participate in the trial or any subject who has a perceived conflict of interest that could impact study outcomes (eg, a subject who may be on disability due to MDD).

Additional Exclusion Criteria Assessed at the Week 8 Visit for Continuation in Phase B

32) Subjects who do not meet predetermined blinded criteria for inadequate response.
33) Subjects with a positive result for THC or illicit drugs at the Week 6 visit. Subjects with a positive urine drug screen at Week 6 due to prescription or over-the-counter medications or products and/or a positive blood alcohol result at Week 6 may proceed to randomization only after consultation and approval by the medical monitor.

CCI



A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to restrictions to medications and lifestyle described in Section 6.5 and Section 5.3, respectively.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Not applicable.

5.3.2 Caffeine, Alcohol, and Tobacco

Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial. The investigator may request a blood alcohol or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.

5.3.3 Activity

Subjects should not significantly alter their current activity levels or exercise routines. They should be encouraged to maintain their usual levels of physical activity throughout the trial.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an informed consent form [ICF]), but who is not enrolled or assigned ADT. All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespectively of IMP administration.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in eSource:

- Date of informed consent
- Visit date (screening visit)
- Demographics (collection date, birth date, sex at birth, race, ethnicity, country)
- Screen failure date
- Reason for screen failure
- Any AEs

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened, except for those subjects who test positive for THC or illicit drugs. The medical monitor must be contacted before rescreening any subjects who initially failed screening due to a positive blood alcohol test or positive drug screens resulting from use of prescription or over-the-counter medications or products. In the event that the subject is rescreened for trial participation, and the rescreening was not completed within the original screening window, a new ICF must be signed.

6 Trial Intervention(s) and Concomitant Therapy

6.1 Trial Intervention(s) Administered

Trial interventions are all prespecified, investigational and noninvestigational interventions intended to be administered to the subjects during the conduct of the trial.

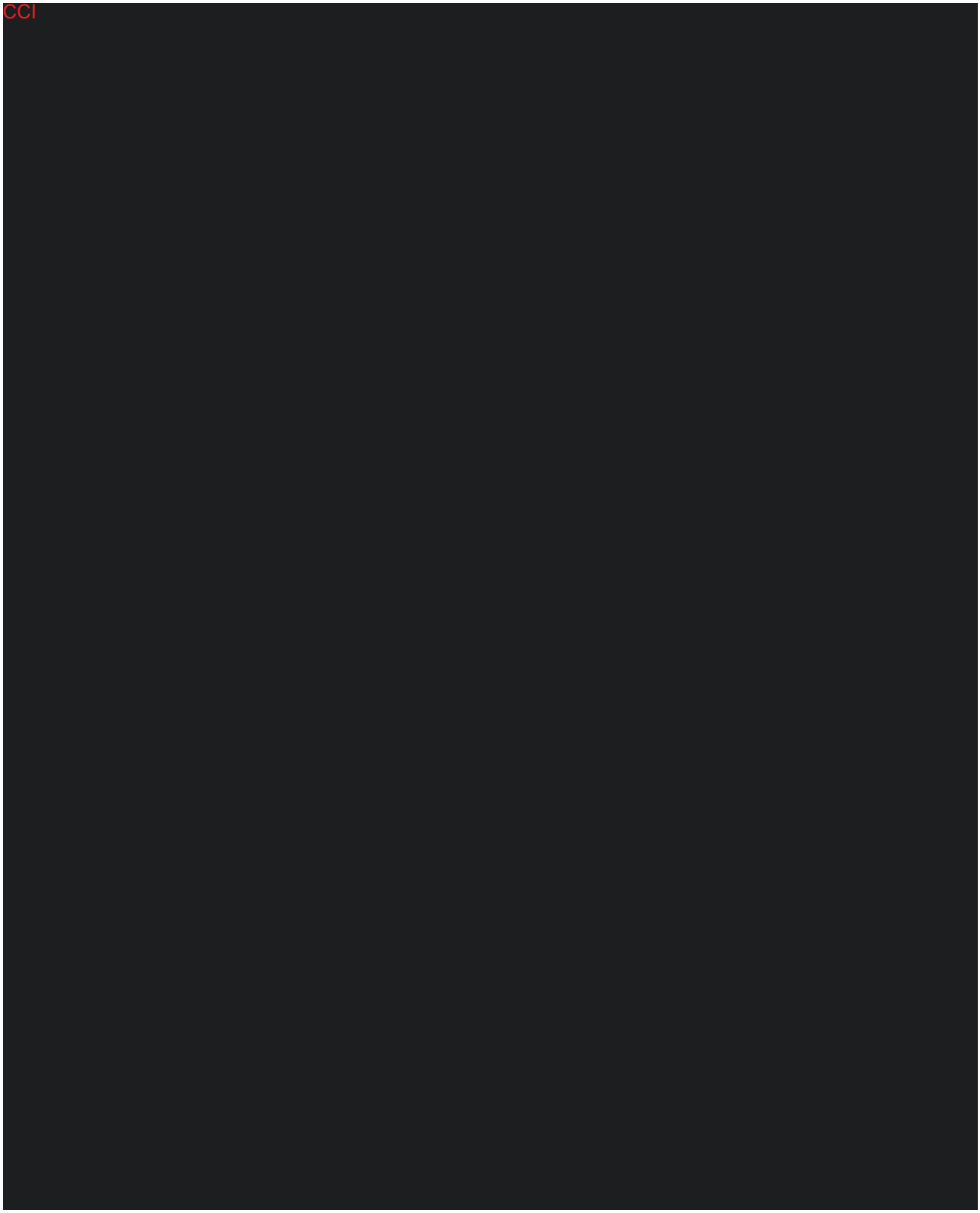
This trial is not a low-interventional trial as SEP-363856 is not marketed/authorized.

6.1.1 Phase A - Single-blind Prospective Treatment Phase (All Subjects – Baseline to Week 8)

CCI



CCI



CCI

[redacted]

6.1.1.1 Administration of SEP-363856 With CYP2D6 Inhibitors

SEP-363856 is partially metabolized through CYP2D6, and since several antidepressant drugs are inhibitors of this metabolic pathway, an understanding of this interaction is important. An open-label, drug-drug interaction trial (SEP361-109) was conducted in healthy adults with a CYP2D6 extensive metabolizer (EM) phenotype to investigate the pharmacokinetics (PK) and safety of SEP-363856 following oral administration of SEP-363856 (25 mg/day) on Days 1 and 11 without or with a strong CYP2D6 inhibitor (paroxetine [20 mg/day, administered from Day 5 to Day 14]). Coadministration of SEP-363856 with paroxetine increased the area under the concentration-time curve calculated from time zero to infinity ($AUC_{0-\infty}$) and maximum (peak) plasma concentration of the drug (C_{max}) of SEP-363856 by 72% and 31%, respectively. Mean trough concentrations of paroxetine kept increasing through Day 15 but appeared to be reaching steady-state by Day 12. Paroxetine plasma concentrations after 20 mg (once daily dosing) were consistent with literature reports and considered to be sufficient for CYP2D6 inhibition.[25,26] Therefore, no additional CYP2D6 inhibition would be expected with higher paroxetine doses. SEP-363856 was generally well-tolerated when administered as a single dose of 25 mg with 20 mg paroxetine by the healthy subjects in this trial. Based on these results, it is considered appropriate that when SEP-363856 is coadministered with strong CYP2D6 inhibitors (eg, antidepressant drugs paroxetine, fluoxetine), a dose reduction of SEP-363856 (or matching placebo) should only be necessary and made if adverse effects are observed.

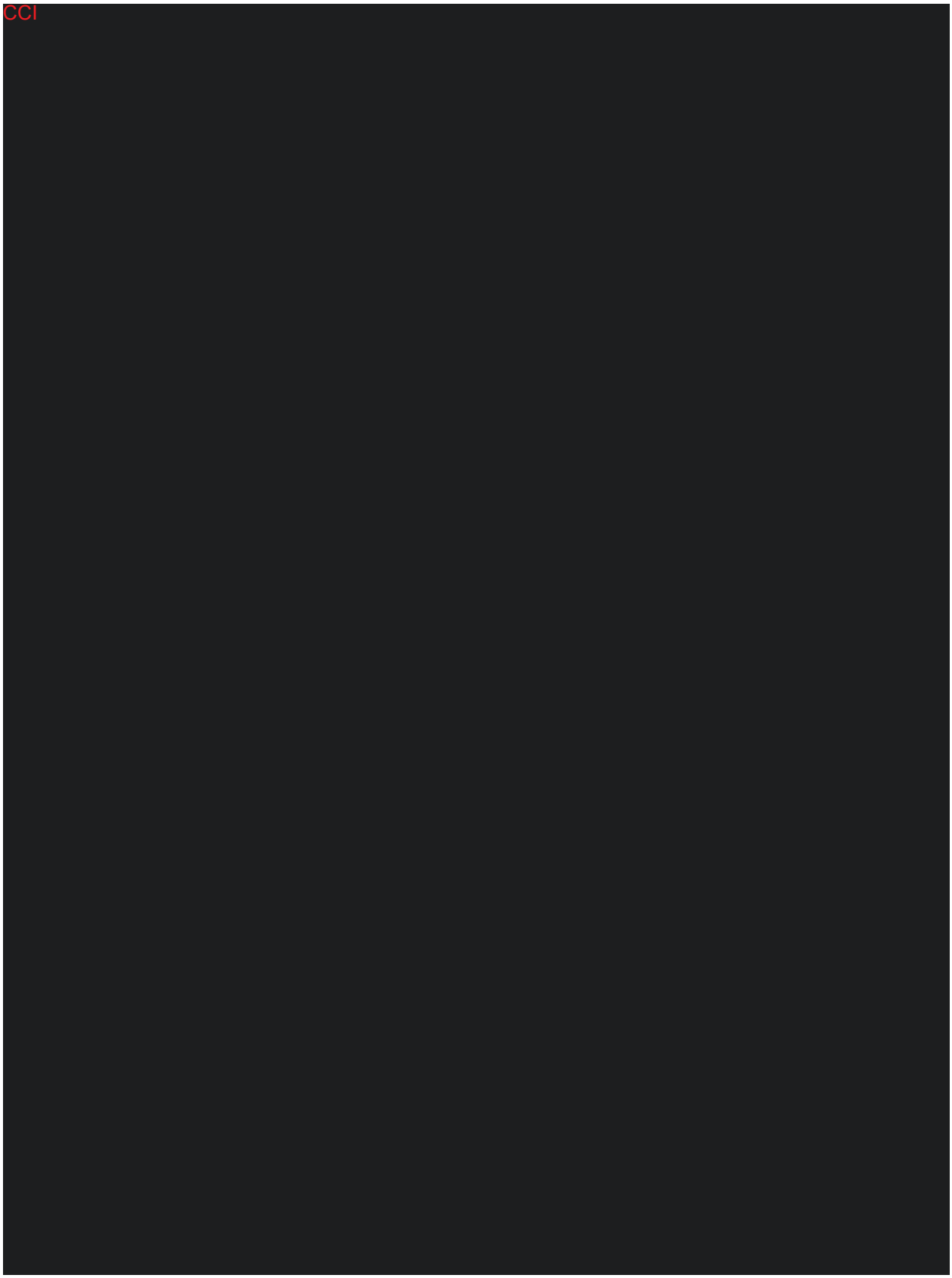
6.1.1.2 Dosing Schedules for Each Antidepressant Therapy

The sections below outline the dosing schedule during Phase A for each assigned open-label ADT.

CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI



6.1.2 Phase B - Double-blind Randomization Phase (Inadequate Responders)

At the Week 8 visit, subjects with an inadequate response to prospective treatment with ADT (ie, meet blinded score-based criteria for inadequate response) who are otherwise eligible for randomization (see exclusion criteria #32 to #35 in Section 5.2.2) will be randomized into Phase B and will receive 1 of the following double-blind treatment regimens:

- Continued placebo + ADT (that is, placebo plus the final dosage of the assigned open-label ADT reached during Phase A), or
- SEP-363856 + ADT (50 to 75 mg/day, plus the final dosage of the assigned open-label ADT reached during Phase A).

Treatment assignments will be obtained from the integrated eSource. The fixed-block, computer-generated randomization schedule will be stratified by trial center and designed to allocate subjects to a treatment regimen in a 1:1 ratio. Neither the investigator nor the subject will be aware of the treatment assignment.

Dispensing of blinded IMP and ADT in Phase B will take place at the time points described in the schedule of assessments (Table 1.3-2).

All doses of SEP-363856 and matching placebo should be taken orally at approximately the same time each evening at bedtime and can be administered without regard to meals. The assigned ADT should be taken orally and dosed at approximately the same time each day. It is preferred that the subject take the ADT dose at the same time as the blinded IMP in the evening. Subjects must continue on the same ADT that was assigned in Phase A at the final dose taken in Phase A.

The dosing scheme for Phase B is presented in Table 6.1.2-1. The initial dose of SEP-363856 dispensed to randomized subjects at the Week 8 visit will be 25 mg SEP-363856 (or matching placebo). The dose of SEP-363856 will then be increased to 50 mg four days after the Week 8 visit and all subjects will receive 75 mg by the Week 9 visit.

Subjects who experience dose-related tolerability issues at the 75 mg dose of SEP-363856 may decrease to 50 mg at any time after the Week 9 visit (via a scheduled or unscheduled visit).

Increases (rechallenge) in the dose of SEP-363856 (from 50 to 75 mg/day) can be made at Week 10, 11, or 12. The dose of SEP-363856 cannot be increased after the Week 12 visit.

Subjects must return to the trial site clinic for unscheduled visits if dose reductions for SEP-363856 are required between scheduled visits.

Subjects unable to tolerate the 50 mg dose of SEP-363856 (or matching placebo) will be withdrawn from the trial.

Table 6.1.2-1 Daily Dosing Scheme for SEP-363856 or Matching Placebo in Phase B

Treatment Arm	Trial Visit						
	Week 8 Days 1 to 3	**Week 8 Days 4 to 7**	**Week 9[a] Day 8**	**Week 10[b]**	**Week 11[b]**	**Week 12[b]**	**Week 13[c]**
SEP-363856	25 mg	50 mg	75 mg	75 or 50 mg	75 or 50 mg	75 or 50 mg	75 or 50 mg
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

[a]All subjects will receive 75 mg SEP-363856 (or matching placebo) by Week 9. Subjects who experience dose-related tolerability issues at the 75mg dose of SEP-363856 may decrease 50 mg at any time after the Week 9 visit (via a scheduled or unscheduled visit).

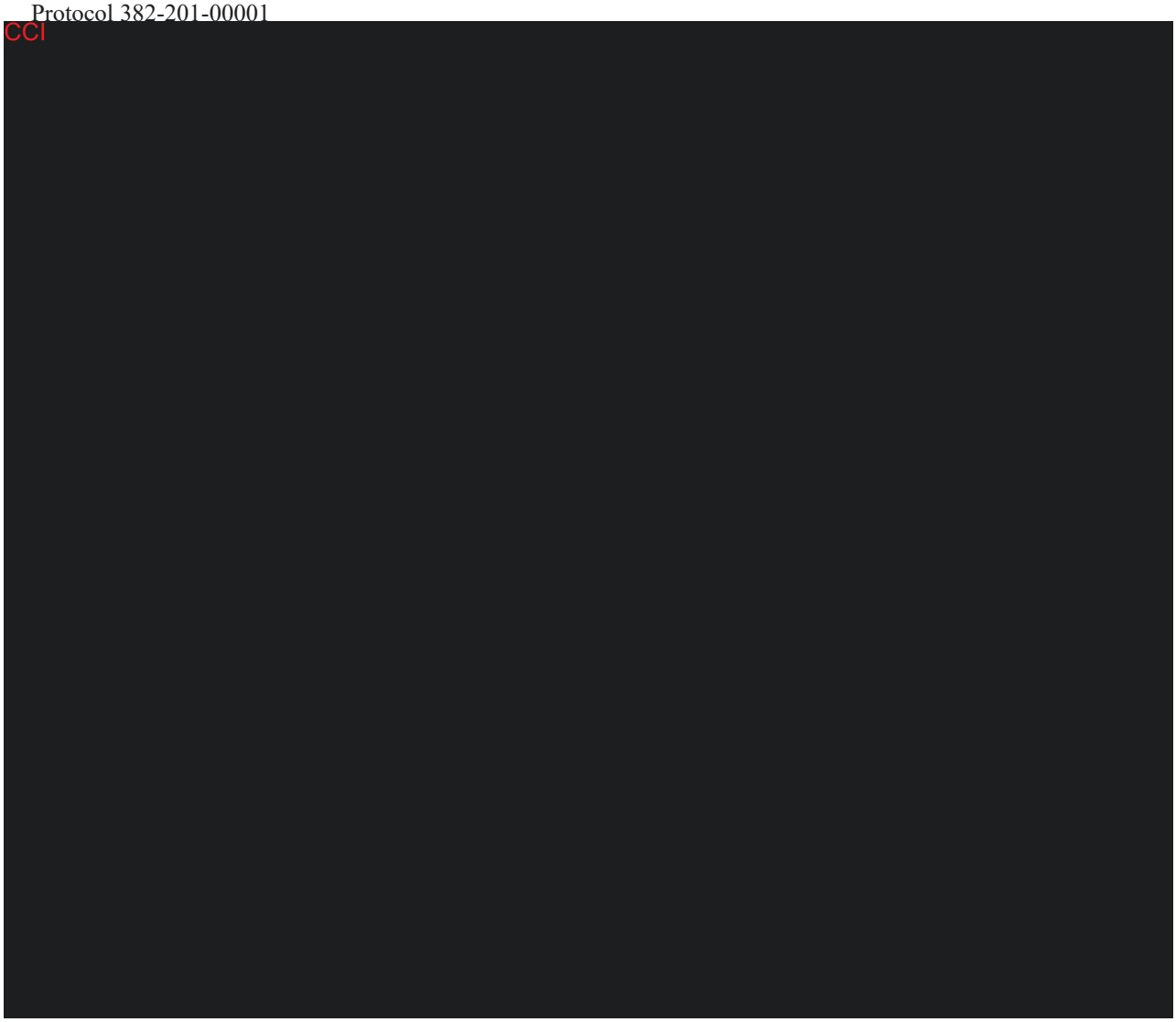
[b]Increases (rechallenge) in the dose of SEP-363856 (from 50 to 75mg/day) can be made at Week 10, 11, or 12. Dose rechallenges are not permitted at unscheduled visits. Subjects unable to tolerate the 50 mg dose of SEP-363856 (or matching placebo) will be withdrawn from the trial. Subjects must return to the trial site clinic for unscheduled visits if dose reductions for SEP-363856 are required between scheduled visits.

[c]The dose of SEP-363856 cannot be increased after the Week 12 visit, but can be decreased to 50 mg at any time (scheduled or unscheduled visits) after Week 9.

In summary, the dosing scheme is flexible and includes potential doses of 50 or 75 mg SEP-363856 (or matching placebo).

No dose adjustments to ADTs are permitted during Phase B of the trial.

CCI



6.1.4 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on SEP-363856 management, please refer to the IB.

6.2.1 Packaging and Labeling

Investigational medicinal product will be provided by the clinical trial sponsor or designated agent to the investigators and the persons designated by the investigator(s) or institution(s). SEP-363856 and placebo will be supplied as blister cards and ADT will be supplied in bottles. Each blister card and bottle used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, the clinical trial sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements and other information required by local regulatory authorities.

6.2.2 Storage

The trial intervention (SEP-363856, placebo, and ADT) will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees.

The trial intervention will be stored according to the conditions indicated on the labels.

The trial site staff will maintain a temperature log in the trial intervention storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of trial intervention received, dispensed, administered, and destroyed. Neither the investigator nor any designees may provide trial intervention to any subject not participating in this protocol.

6.2.4 Returns and Destruction

The trial intervention may only be destroyed by the trial site(s), if approved by the clinical trial sponsor and if the trial intervention destruction meets all local regulations. The trial intervention will be destroyed by the clinical trial site following completion and verification of accountability of the trial intervention by the assigned trial monitor. The trial site(s) may utilize qualified third-party vendors for trial intervention destruction. A certificate of destruction should be filed within the trial intervention accountability.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, clinical trial subject, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device or medicinal product or a falsified, tampered, or diverted product after it is released for distribution to a clinical trial.

Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product or medical device to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the trial intervention from the clinical trial sponsor or clinical trial sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the clinical trial sponsor (or clinical trial sponsor's designee) within 24 hours of becoming aware of the PQC according to the procedure outlined below.

Send PQC reporting information to the Otsuka Pharmaceutical Development & Commercialization, Inc PQC complaints mailbox e-mail: CCI [redacted]. Also indicate whether or not the complaint sample is available for return.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow the reporting mechanism above.

6.2.5.2 Information Required for Reporting Purposes

The following information is required for reporting purposes:

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return
- Was any subject at risk due to the identified issue?

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the clinical trial sponsor will provide return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample for a dispensed kit has been forwarded to the clinical trial sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the clinical trial sponsor.

6.3 Measures to Minimize/Avoid Bias

During the entire trial, treatment with ADT will be open-label. The investigator and the subject will have knowledge of the assigned treatment.

During the single-blind prospective treatment phase (Phase A) and during additional treatment with placebo + ADT for those subjects not randomized into Phase B (ie, Phase A+), treatment with placebo will be single-blind, meaning that the investigator, but not the subject, will have knowledge of the treatment assignment (ie, placebo).

During the Randomization Phase (Phase B), IMP will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment (ie, placebo or SEP-363856). Treatment assignments will be based on a computer-generated randomization code provided by the clinical trial sponsor. Clinical trial sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, and reporting SAEs to regulatory agencies.

Procedures for breaking the blind can be found in Section 8.7.7.

6.4 Subject Compliance

Responsible trial personnel will dispense SEP-363856/matching placebo and ADTs. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking trial intervention as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also noncompliant and should be considered for discontinuation. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

6.5 Concomitant Medications or Therapies

The investigator will record all medications (including prescription medications, over-the-counter medications, herbal remedies, etc.) and therapies taken by the subject from 30 days prior to signing the informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in eSource. The investigator will also record all medications and

therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in eSource.

For concomitant medications, the following will be recorded in eSource: medication, indication, dose, frequency, route, start date, and end date. For concomitant therapy, the following will be recorded in eSource: therapy, indication, start date, frequency, and end date.

6.5.1 Prohibited Medications or Therapies

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. Table 6.5.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP in Phase A. Subjects who are receiving an ADT at screening are required to washout from the current ADT for a minimum of 24 hours before receiving the first dose of investigator-assigned ADT in Phase A. In instances where a subject will be assigned to the same ADT in Phase A, the 24-hour washout period is not necessary (ie, a prior course of treatment with 1 of the protocol-specified ADTs that was at an adequate dose per the MGH-ATRQ, but of insufficient duration).

Table 6.5.1-1 List of Medications Prohibited Before the Trial

1.	Neuroleptic agents (depot or long-acting injectable)	Exclusionary
2.	Monoamine oxidase inhibitors	CCI [redacted]
3.	Neuroleptic agents (oral)	
4.	Benzodiazepines	
5.	Hypnotics, including nonbenzodiazepine sleep aids	
6.	Ketamine, esketamine, arketamine, or psychedelic therapy	Exclusionary for the treatment of depression or any other psychiatric condition during the current MDE

CCI [redacted]

Table 6.5.1-2 lists all other medications/therapies prohibited during the trial, including exceptions, where appropriate.

Table 6.5.1-2 List of Medications/Therapies Prohibited During the Trial

1.	All psychotropic agents including, but not limited to, the following: a) Neuroleptic agents, including oral and depot or long-acting injectable formulations. b) Anticonvulsants. c) Antidepressants other than those prescribed as ADT during the trial. d) Mood stabilizers (ie, lithium). e) Benzodiazepines, except when used to manage TEAEs such as agitation and anxiety.[a] f) Hypnotics, including ramelteon and other nonbenzodiazepine sleep aids, except for specific medications when used to manage treatment-emergent AEs related to insomnia.[b] g) Stimulants. h) Opioid analgesics, unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and nonprescription herbal preparations with CNS effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, cannabidiol, etc). j) Monoamine oxidase inhibitors k) Ketamine, esketamine, arketamine, or psychedelic therapy
2.	Investigational agents.
3.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.
4.	Any medications that are contraindicated with the use of ADTs per their respective product label.
5.	Initiation of new psychotherapy.

EPS = extrapyramidal symptoms.

[a]Administration of specific oral benzodiazepines is permitted for the short-term management of TEAEs such as anxiety and agitation up to a maximum of 2 mg/day lorazepam (or equivalent) in divided doses. Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg alprazolam = 5 mg diazepam = 0.5 mg clonazepam. The prescribed benzodiazepine should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion and taking into account potential withdrawal effects. Benzodiazepines should not be taken for > 3 consecutive days at any time. Benzodiazepines must not be administered within 8 hours prior to scheduled efficacy and safety assessments, including EPS scales.

[b]Nonbenzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia CCI [redacted] and up to 7 days total in Phase B, but not on the same day as administration of a benzodiazepine, regardless of indication. For the nonbenzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Nonbenzodiazepine sleep aids must not be administered within 8 hours prior to scheduled efficacy and safety assessments, including EPS scales.

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). The investigator should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered nonprescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator. In particular, the investigator should caution the subject about concomitant use of the following during the trial:

- Nonsteroidal anti-inflammatory drugs, aspirin, or other drugs that interfere with coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of upper gastrointestinal bleeding.[27]
- Triptans (eg, sumatriptan, naratriptan, almotriptan, frovatriptan, rizatriptan, eletriptan, and zolmitriptan), linezolid, and methylene blue since there have been rare postmarketing reports of serotonin syndrome or serotonin syndrome-like reactions (eg, mental status changes, hyperreflexia, autonomic effects, lack of coordination, and diarrhea) following the concomitant use of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors and these drugs.[28,29]

Electroconvulsive therapy is prohibited for the current MDE or within 1 year of the screening visit, whichever is longer, and for the duration of the trial. Neuromodulation treatment such as transcranial magnetic stimulation is also prohibited during the current MDE. In addition, subjects may not undergo implantation of a device for vagus nerve stimulation or deep brain stimulation during the trial or ever had a device implanted for management of treatment resistant depression in the past.

Use of intramuscular benzodiazepines is prohibited throughout the trial. Continual use of oral benzodiazepines is also not permitted during the trial (benzodiazepines should not be taken for > 3 consecutive days at any time) and subjects must discontinue benzodiazepines for at least 7 days prior to the baseline visit. However, administration of specific oral benzodiazepines is permitted for the short-term management of TEAEs such as anxiety and agitation up to a maximum of 2 mg/day lorazepam (or equivalent) in divided doses. Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg, alprazolam = 5 mg diazepam = 0.5 mg clonazepam. The prescribed benzodiazepine should be discontinued

as soon as the AE for which it was initiated subsides, as per the investigator's discretion, and taking into account potential withdrawal effects.

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc.) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.

6.5.2 Permitted Medications or Therapies

Escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, and venlafaxine are protocol-defined ADTs in this trial (see Section 6.1.1).

Nonbenzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia for up to [redacted] up to 7 days total in Phase B, but not on the same day as administration of a benzodiazepine, regardless of indication. For the nonbenzodiazepine sleep aids, trial sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia.

Benzodiazepines, nonbenzodiazepine sleep aids, must not be administered within 8 hours prior to scheduled efficacy and safety assessments, including extrapyramidal symptoms (EPS) scales. Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration in eSource.

As described in Section 6.1.1.1, caution should be taken when SEP-363856 is coadministered with strong CYP2D6 inhibitors, and a dose reduction should be considered if adverse effects are observed. Subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they have been participating in the therapy regularly (eg, weekly) for at least 90 days prior to screening and commit to maintain their participation during the course of the trial at the current frequency.

All trial personnel should be familiar with the content of the IB for SEP-363856 in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Discontinuation of Trial/Treatment and Subject Discontinuation/Withdrawal

7.1 Entire Trial or Treatment

If the clinical trial sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, institutional review boards (IRBs)/independent ethics committees (IECs), and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the clinical trial sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the clinical trial sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

7.3 Discontinuation of Trial Intervention

Under certain circumstances, it may be necessary for a subject to permanently discontinue trial intervention. See the schedules of assessments (Table 1.3-1 and Table 1.3-2) for data to be collected at the time of discontinuation of trial intervention and follow-up and for any further evaluations that need to be completed. If a subject discontinues trial intervention due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

For each subject who discontinues trial intervention, the main reason for discontinuation will be recorded in eSource.

7.3.1 Interruption of Trial Intervention

All attempts should be made to avoid treatment interruptions during the trial. If a subject's IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery; dental work, or

a temporary situation that prevents subject compliance with the IMP dosing schedule), the subject's IMP should be resumed as early as the situation allows.

If > 4 consecutive doses of IMP are missed, a discussion should occur with the medical monitor to determine if the subject should be discontinued from the trial as a result of the treatment interruption.

7.3.2 Rechallenge

As described in Section 6.1.2, increases (rechallenge) in the dose of SEP-363856 (from 50 to 75 mg/day) during Phase B can be made at Week 10, 11, or 12 if the dose had previously been decreased to 50 mg/day .

7.4 Subject Discontinuation/Withdrawal From the Trial

- A subject may withdraw from the trial at any time at the subject's own request for any reason (or without providing any reason).
- A subject may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the trial, if possible, an ET visit should be conducted, as shown in the schedules of assessments. See the schedules of assessments (Table 1.3-1 and Table 1.3-2) and the text below for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.
- If a subject withdraws consent from the trial, the subject will be permanently discontinued from all trial interventions and the trial.
- If the subject withdraws consent for disclosure of future information, the clinical trial sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a subject withdraws from the trial, the subject may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial site staff, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.

- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue trial intervention administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

CCI [redacted]

7.4.1 Documenting Reasons for Subject Discontinuation/Withdrawal

A subject may discontinue IMP for the reasons listed below:

- Adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Failure to meet trial continuation criteria at Week 8
- Lack of efficacy
- Lost to follow-up
- Noncompliance with IMP
- Physician decision

- Pregnancy (see Section 10.3)
- Protocol deviation
- Trial site terminated by the clinical trial sponsor
- Trial terminated by the clinical trial sponsor
- Withdrawal by subject
- Other

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

7.4.2 Options for Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.5 Lost to Follow-up

Subjects who cannot be contacted on or before the follow-up visit, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

If the subject was classified as "lost to follow-up", "Were you able to contact the subject?", "Date of contact/Date of final contact attempt" and "Contact method" will be recorded in eSource.

8 Trial Procedures

8.1 Efficacy Assessments

It is required that trained and experienced clinicians administer all rating scales. The number of raters within each trial center should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training, certification, and materials for rating will be provided by the clinical trial sponsor or designee.

Efficacy assessments should be completed prior to safety assessments and CCI [redacted]

Quality reviews of audio recording may be performed for some assessments, including eligibility review, in order to verify the quality of the assessment/interview and accuracy of scoring.

8.1.1 Montgomery Åsberg Depression Rating Scale

The MADRS will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2). It is strongly recommended that the MADRS be conducted as the first clinical assessment at each visit where it is performed.

The MADRS[30] will be utilized as the primary efficacy assessment of the subject's level of depression and must be administered utilizing the Structured Interview Guide for the MADRS (SIGMA).[31] Detailed instructions for administration of this structured interview will be provided. The MADRS consists of 10 items, each rated from 0 to 6. A higher score on the MADRS represents a higher severity of the level of depression.

8.1.2 Clinical Global Impression - Severity of Illness

The Clinical Global Impression - Severity of Illness (CGI-S) will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

The severity of illness for each subject will be rated using the CGI-S.[32] The CGI-S is a standardized, clinician-administered global rating scale that measures disease severity on a 7-point Likert scale. A higher score on the CGI-S represents a higher severity of disease. To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

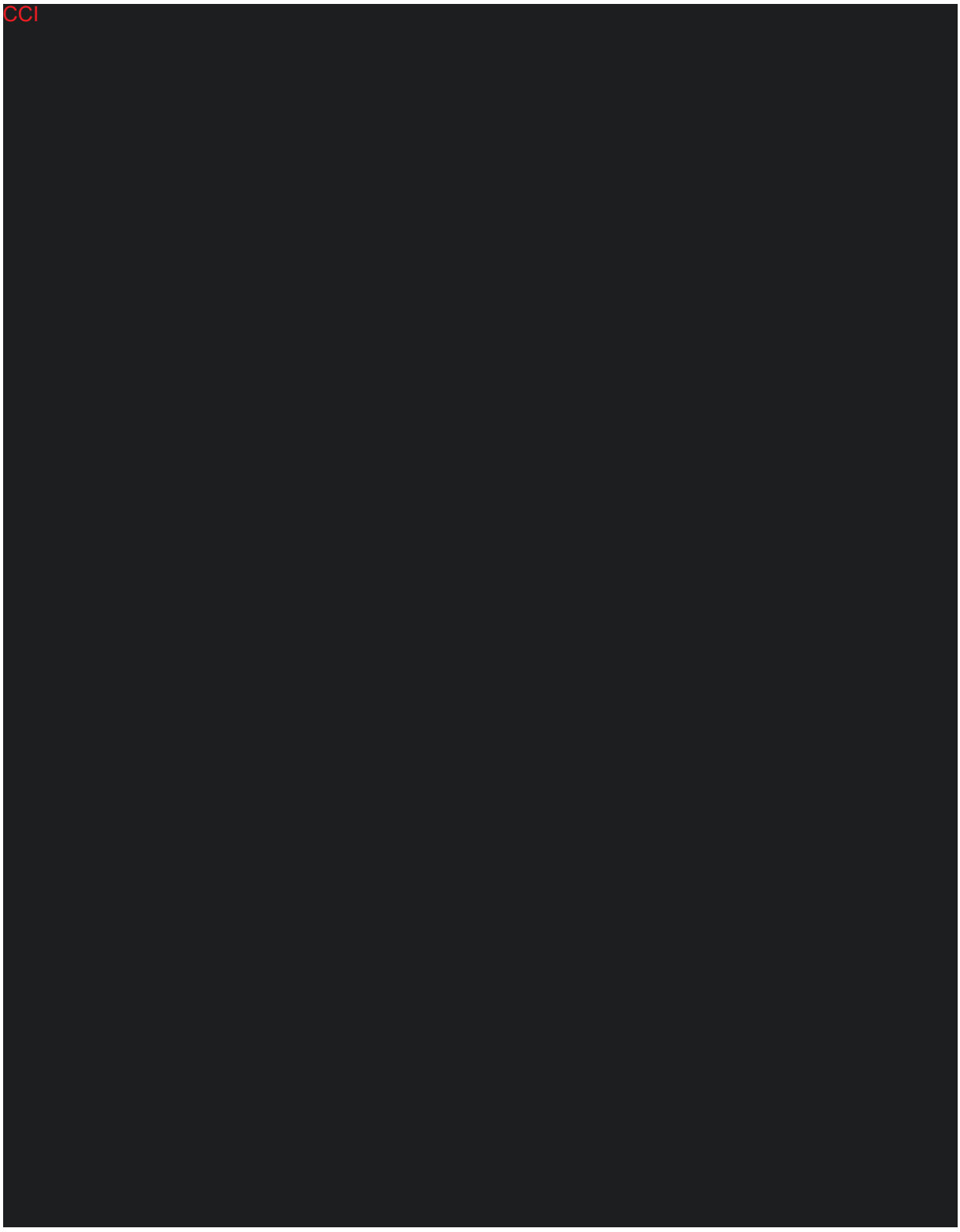
CCI

[redacted]

CCI

[redacted]

CCI



CCI



8.6 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.7.

8.6.1 Clinical Laboratory Assessments

Clinical laboratory assessment samples will be collected at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2) to perform the clinical laboratory assessments described in Section 10.2.

Only if results are exclusionary at screening (see Section 5.2.2), will a repeat test be performed prior to the baseline visit; the results must be available and inclusionary prior to randomization.

Subjects with a positive urine drug screen for illicit drugs other than cannabis are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of cannabis, prescription, or over-the counter medications or products, and/or a positive blood alcohol result that in the investigator's documented opinion does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, may continue evaluation for the trial following consultation and approval by the medical monitor. Note that subjects testing positive for THC at the screening visit must agree to abstain from use of cannabis products for the duration of the trial and must test negative for THC prior to the completion of the screening period. These subjects must also test negative for THC at the baseline visit

prior to enrollment. Additionally, subjects who test positive for THC at Week 6 will not be permitted to enter Phase B of the trial.

Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment.

Reports from laboratory tests will be assessed by the investigator or qualified designee for clinical significance.

Additional urine drug assessments can be conducted at any time at the discretion of the investigator.

8.6.2 Physical Examination

Physical examinations will be performed at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

A complete physical examination will be performed at screening and will consist of measurement of height, body weight, and waist circumference and a review of the following body systems: head, ears, eyes, nose and throat, thorax, abdomen, urogenital (as indicated), extremities, neurological, and skin and mucosae. Repeat measurements of height is not required at the physical examinations scheduled after screening. Weight and waist circumference will be measured at each physical examination.

The principal investigator or his/her appointed designee is primarily responsible to perform the physical exam. Whenever possible, the same individual should perform all physical examinations.

Directed physical examinations in response to reported AEs will be conducted as necessary.

8.6.3 Vital Signs

Vital signs will be collected at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

Vital signs include blood pressure, heart rate, and body temperature. Blood pressure and heart rate measurements will be taken in a supine and standing position. Blood pressure and heart rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and heart 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 heart rate throughout the trial. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, their supine and standing blood pressure and heart rate should be collected at that

time in the manner described above. Vital signs scheduled at the same visit as blood samples are to be completed before blood is drawn.

8.6.4 12-Lead Electrocardiogram

Standard 12-lead ECGs will be performed at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2). The ECGs scheduled for the same visit as blood sample collections are to be completed before blood is drawn.

The 12-lead ECG will be performed after the subject has been supine and at rest for ≥ 5 minutes.

The 12-lead ECGs conducted at screening will be performed in triplicate, taken approximately 5 minutes apart. Any screening or baseline ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Any repeated screening ECGs should be performed in triplicate.

All subsequent ECG assessments require a single ECG recording.

The ECG results will be evaluated at the trial site to determine the subject's eligibility and to monitor safety during the trial.

The principal investigator or qualified designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis.

CCI [redacted]

The ECGs scheduled for the same visit as blood sample collections are to be completed before blood is drawn.

8.6.5 Suicidality Monitoring

Suicidality monitoring will occur at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

Suicidality will be monitored during the trial using the C-SSRS. The C-SSRS will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

This trial will use the “Baseline/Screening” and “Since Last Visit” versions of the scale. The “Baseline/Screening” version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. The “Since Last Visit” version will be completed at all visits after screening.

8.6.6 Other Safety Variables

8.6.6.1 Extrapyramidal Symptoms

8.6.6.1.1 Simpson Angus Scale

The Simpson Angus Scale (SAS) will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

The SAS[40] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms, and a score of 4 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items.

8.6.6.1.2 Abnormal Involuntary Movement Scale

The Abnormal Involuntary Movement Scale (AIMS) will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

The AIMS[41] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject’s dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject’s dental status.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

8.6.6.1.3 Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale (BARS) will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

The BARS[42] is defined as the global clinical assessment of akathisia. The BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning.

8.6.6.2 Sexual Function

The Changes in Sexual Functioning Questionnaire (CSFQ) will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

The CSFQ-Short Form[43] is a 14-item questionnaire that produces an overall measure of sexual functioning as well as scores on 2 sets of subscales: a set of 5 scales corresponding to important dimensions of sexual functioning and a set of three scales corresponding to the three phases of the sexual response cycle.

8.6.6.3 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) will be administered at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2).

The PSQI contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form 7 “component” scores, each of which has a range of 0 to 3 points. In all cases, a score of “0” indicates no difficulty, while a score of “3” indicates severe difficulty. The 7 component scores are then added to yield one “global” score, with a range of 0 to 21 points, “0” indicating no difficulty and “21” indicating severe difficulties in all areas.

8.7 Adverse Events

8.7.1 Definitions

Investigational medicinal product: IMP is defined as a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. SEP-363856 and placebo are the IMP in this trial.

Auxiliary medicinal product (AxMP): AxMP is defined as a medicinal product used for the needs of a clinical trial, but not an IMP. In this trial, authorized ADTs are considered as AxMP, as they are used as background therapy in the management of MDD. A list of the ADTs to be administered in this trial is provided in Section 6.1.1.

Medicinal product (MP): The trial interventions (IMP and AxMP) are considered as MP.

Adverse event: An AE is defined as any untoward medical occurrence in a clinical trial subject administered an MP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an MP related to any dose administered.

Suspected adverse reaction: A suspected adverse reaction is any AE for which there is a reasonable possibility that the MP caused the AE. For the purpose of investigational new drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the MP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

Treatment-emergent AEs: Treatment-emergent adverse events are defined as AEs with an onset date on or after the start of double-blind treatment. In more detail, TEAEs are all AEs which started after the start of double-blind MP treatment; or if the event was continuous from baseline and was worsening, serious, MP related, or resulted in death, discontinuation, interruption, or reduction of MP.

Serious adverse event: includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.

- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious adverse events: All AEs that do not meet the criteria for a "serious" AE.

Adverse events of special interest: These AEs may warrant collection of additional information across the entire trial population to better characterize these events.

Immediately reportable event:

- Any SAE with MP.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.7.6).
- Pregnancies are also defined as immediately reportable events (IREs). Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the clinical trial sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the AE eSource form if the pregnancy occurs in a female subject and there is an abnormality or complication.

Clinical laboratory test value changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject as they become available. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in eSource. The severity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

Causality: Assessment of causal relationship of an AE to the use of the MP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the MP and the AE.
Not Related:	There is no temporal or causal relationship between the MP and the AE.

CCI [redacted]. In Phase B (randomized, double-blind portion of the trial), investigators will assess MP causality based on SEP-363856/matching placebo.

8.7.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded in the eSource provided by the clinical trial sponsor. Adverse event collection will begin after a subject signs the ICF, and will continue until the follow-up visit (7 ± 2 days after the last dose of IMP). All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespective of MP administration.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Additional information will be collected for the non-serious psychiatric AEs that led to discontinuation from the study as well as all serious psychiatric AEs within the study.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the clinical trial sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 8.7.3. Special attention should be paid to recording hospitalization and concomitant medications.

The adverse event, start date, end date, seriousness, severity, relationship to trial intervention (MP causality), action taken with trial intervention, and outcome will be recorded in eSource.

8.7.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE with MP, AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy), by telephone, fax, or e-mail to the clinical trial sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eSource). Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding safety information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.7.8.2.

8.7.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.7.5 Adverse Events of Special Interest

Not applicable, no adverse events of special interest (AESI) have been identified.

8.7.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE in eSource.

8.7.7 Procedure for Breaking the Blind

The investigator is encouraged to contact the clinical trial sponsor/CRO medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the clinical trial sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the clinical trial sponsor/CRO medical advisor).

The investigator must contact the clinical trial sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, Syneos Health Pharmacovigilance & Drug Safety must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

8.7.8 Follow-up of Adverse Events

8.7.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the clinical trial sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.7.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 7 ± 2 days after the last dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eSource form and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the clinical trial sponsor and recorded on the AE eSource form and the IRE form, according to the appropriate reporting procedures described in Section 8.7.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the clinical trial sponsor. The investigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- The subject is lost to follow-up, or
- Has died.

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the clinical trial sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

8.7.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the clinical trial sponsor according to the procedures outlined in Section 8.7.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the clinical trial sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.8 Treatment of Overdose

Potential overdose to SEP-363856 has not been evaluated. The effects of an overdose of SEP-363856 are unknown and there is no known treatment in case of overdose. Appropriate supportive measures should be instituted, and close medical supervision and monitoring should be used in the case of pharmacological effects or overdose until the subject recovers. Consider the possibility of multiple-drug overdose.

8.9 Subject Assessment Recording

Subject assessment recording is described in Section 8.1.6.

8.10 Other Assessments

8.10.1 Structured Clinical Interview for *DSM-5*, Clinical Trials Version

The SCID-5-CT will be used as a tool for conducting a structured interview for eligibility assessment at the screening visit (Table 1.3-1).

The SCID-5-CT is a modified version of the SCID developed for use in clinical trials. It is a semi-structured interview for the purpose of making a *DSM-5* diagnosis (First-2015). Clinicians administering the SCID should be familiar with the *DSM-5* classification and diagnostic criteria.

8.10.2 Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The MGH-ATRQ will be used to collect a subject's history of pharmacological treatment for their current MDE. It will be administered at screening as part of the collection of the subject's psychiatric history and will be utilized to determine eligibility for entry into the trial.

9 Statistical Considerations

9.1 Sample Size

The primary efficacy endpoint is the change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in MADRS total score. The trial will compare the placebo + ADT arm to the SEP-363856 + ADT arm, randomized at a ratio of 1:1, with an overall alpha of 0.05 for the primary endpoint.

The sample size is calculated based on a CCI [redacted]

CCI [redacted]

9.2 Datasets for Analysis

The following analysis sets are defined for this trial:

- Enrolled Analysis Set: all subjects who signed an ICF for the trial and enrolled into Phase A.
- ADT Analysis Set: all subjects who took at least 1 dose of ADT in Phase A.
- Randomized Analysis Set: all subjects who were randomized in Phase B.
- Safety Analysis Set: all randomized subjects in Phase B who received at least 1 dose of double-blind IMP. Subjects will be excluded from this population only if there is documented evidence (ie, drug dispensed = drug returned or no IMP dispensed) that the subject did not take IMP. If a subject is dispensed IMP and is lost to follow-up, he/she will be considered exposed.
- Full Analysis Set (FAS): The FAS includes all subjects in the Safety Analysis Set in Phase B, who have an end of Phase A (ie, Week 8) MADRS assessment.

CCI

The core dataset for all efficacy analyses is the FAS, which is created based on the intent-to-treat (ITT) principle.

9.3 Handling of Missing Data

The mixed-model repeated measures (MMRM) assumes data are missing at random (MAR), which is a reasonable assumption in longitudinal clinical trials in MDD.[44] However, the possibility of "missing not at random" (MNAR) data can never be ruled out. For the primary analysis of the primary endpoint, unobserved future data after participant discontinuation due to lack of efficacy and AE will be imputed using placebo-based multiple imputation under the MNAR assumption. As sensitivity analyses, either selection model[45] pattern mixture model[46,47,48,49] or shared parameter model[50] will be used to explore data missing mechanisms of MNAR and investigate the response profile of dropout reason. Pattern Mixture Models based on multiple imputation (MI) with mixed missing data mechanisms will be used to investigate the response profile of dropout subjects by last dropout reason under MNAR mechanism for the following 3 scenarios: 1) Dropout reasons due to either AE or lack of efficacy (LOE) as MNAR, 2) Dropout reasons due to either AE or LOE or subject withdrew consent as MNAR, 3) All dropouts as MNAR using Delta adjustment imputation method which is to departure from MAR assumption by progressively increasing the delta until conclusion from the primary analysis is overturned, and 2 scenarios: 1) Dropout reasons due to either AE or LOE or subject withdrew consent as MNAR, 2) All dropouts as MNAR will also be investigated using placebo-based imputation methods in which missing data for both placebo and drug group are imputed based on the imputation model derived from placebo data. If the drug improves outcomes prior to drop out, this benefit is carried into subsequent imputed values, but will diminish over time in accordance with the correlation structure. Details of these exploratory analyses will be provided in the Statistical Analysis Plan (SAP).

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

Based on historical trials in Brexpiprazole aMDD indication (Trials 331-13-214[51] 331-10-227[52] 331-10-228[53] 331-12-282[54]) as an adjunctive therapy to antidepressants for the treatment of MDD in adults, we expect the response profiles to be similar between

dropouts and completers. The drop-out rate should be low based on the historical data, and we will closely monitor dropout rate with blind data. The primary estimand defining the treatment effect of interest uses the hypothetical strategy specified in the International Council for Harmonisation (ICH) E9 Addendum. The estimand, or target of estimation, following the hypothetical strategy is the treatment effect seen, assuming no withdrawals occurred. Subjects who withdraw from IMP treatment either could have lost their treatment effect, had the subjects not taken any other treatment after withdrawal, or could have their treatment effect been masked, had the subjects taken other treatment after withdrawal. This means that any observations made after subjects stop IMP will most likely not contribute relevant information about the treatment effect of the drug. Due to this strategy, the last efficacy assessment after premature trial discontinuation will be performed only at the ET visit. Every effort will be made to complete all of the ET evaluations prior to administering any additional medications for the treatment of MDD or other prohibited medications. In the case of terminal or lost to follow-up events, no ET evaluations would be expected, and only scheduled assessments would be performed before such an event occurred.

The primary estimand for this trial is defined by the following components:

- Population: all subjects with MDD who meet the inclusion/exclusion criteria. For the efficacy analyses, the FAS will be used to represent the population of interest. Further details can be found in SAP.
- Endpoint: the change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in MADRS total score.
- Intercurrent Events: Intercurrent events refer to premature treatment discontinuation (ie, early dropout) prior to end of Phase B (Week 14 visit) attributable to AEs, lack of efficacy, withdrawal of consent, or any other causes.
- Treatment condition: one of the randomized treatment groups of the following per protocol: SEP-363856 (50 to 75 mg/day) + ADT or placebo + ADT.
- Population-level summary: difference in mean change of MADRS total score between two arms.

For the primary analysis of the primary endpoint, unobserved future data after participant discontinuation due to lack of efficacy and AE will be imputed using placebo-based multiple imputation under the MNAR assumption. Unobserved data after participant discontinuation due to other reasons will be analyzed under missing at random assumption. The resulting multiple imputed datasets will then be analyzed using a MMRM and the results will be combined using Rubin’s rules.

For randomized participants who have baseline but do not have any post-baseline MADRS total score, missing post-baseline data will be imputed using a standard MAR-based multiple imputation approach from PROC MI, except for participants who discontinue due to lack of efficacy and AE. For those participants missing due to lack of efficacy and AE, missing post-baseline data will be imputed using placebo-based multiple imputation under the MNAR assumption.

The null hypothesis of the statistical test comparing SEP-363856 + ADT and placebo + ADT, based on the primary efficacy endpoint, is that the change in MADRS total score using SEP-363856 + ADT is equal to the change in MADRS using the placebo + ADT.

$$H0: \Delta\mu_{\text{MADRS SEP-363856 +ADT}} = \Delta\mu_{\text{MADRS placebo +ADT}}$$

$$HA: \Delta\mu_{\text{MADRS SEP-363856 +ADT}} \neq \Delta\mu_{\text{MADRS placebo +ADT}}$$

The objective of the primary analysis is to compare the efficacy of SEP-363856 (50 to 75 mg) to placebo as adjunctive therapy to an assigned open-label marketed ADT in subjects with MDD who demonstrate an inadequate response to a prospective 8-week trial of the same assigned open-label ADT in Phase A. The primary efficacy endpoint is the change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in MADRS total score. For analysis of Phase B data, the end of Phase A measurement is considered as baseline which is defined as the last available measurement prior to the first dose of double-blind IMP in Phase B.

The primary analysis will be performed on the FAS. The primary efficacy analysis will be performed by fitting a MMRM analysis with an unstructured variance covariance structure in which the change from the end of Phase A (Week 8 visit) in MADRS total score (at Weeks 9 to 14) will be the dependent variable. The model will include fixed class effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week. The model will also include the interaction term of end of Phase A (Week 8 visit) values of MADRS total score by visit week as covariates. The primary comparison between the SEP-363856 + ADT group and the placebo + ADT group at Week 14 will be estimated as the difference between least squares (LS) means utilizing the computing software SAS procedure PROC MIXED. The comparison between the SEP-363856 + ADT group and placebo + ADT group will be tested at a significance level of 0.05 (2-sided).

In case there is a convergence problem with MMRM model with the unstructured variance covariance matrix, the following structures other than unstructured will be used in order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry and the first (co)variance structure converging to

the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix. Details of this analysis will be provided in the SAP.

Small centers will be defined as trial sites that do not have at least 2 evaluable subjects (evaluable with regard to the primary efficacy variable) in each treatment arm in Phase B. All small centers will be pooled to form "pseudo centers" for the purpose of analysis according to the following algorithm. Small centers will be ordered from the largest to the smallest based on the number of evaluable subjects. The process will start by pooling the largest of the small centers with the smallest of the small centers until a nonsmall center is formed. This process will be repeated using the centers left out of the previous pass. In case of ties in center size, the center with the smallest center code will be selected. If any centers are left out at the end of this process, they will be pooled with the smallest pseudo centers, or if no pseudo centers exist, they will be pooled with the smallest nonsmall center.

9.4.1.2 Sensitivity Analyses of Primary Endpoint

9.4.1.2.1 Sensitivity Analyses for Missing at Random Assumption

Traditionally the dropout mechanisms are divided into 3 types: (1) missing completely at random (MCAR), in which the probability of dropout doesn't depend on the observed data and the missing data; (2) MAR, in which the probability of dropout depends on the observed data, and (3) MNAR, where the probability of dropout depends on the missing data and possibly the observed data.

Most of MNAR methods have treated all observations with dropout as if they fall within the same dropout type. In practice, different dropout reasons may be related to the outcomes in different ways. Dropout due to an AE and LOE may lead to MNAR dropout. Subjects who withdraw consent may also lead to MNAR dropout. However, it is debatable whether a dropout caused by subject withdrew consent is MAR or MNAR. Except AE, LOE, and subject withdrew consent, all the other dropout reasons may be assumed as either MCAR or MAR dropout.

As sensitivity analyses for MAR assumption, analyses for MNAR will be carried out. Pattern mixture models (PMM) based on MI with mixed missing data mechanisms will be used to investigate the response profile of dropout patients by last dropout reason under MNAR mechanism for the following 3 scenarios:

1) Dropout reasons due to either AE or LOE as MNAR
2) Dropout reasons due to either AE or LOE or subject withdrew consent as MNAR

3) All dropouts as MNAR

9.4.1.2.1.1 Delta Adjustment Imputation Methods

This MNAR sensitivity analysis is a departure from MAR assumption by progressively increasing the delta until the conclusion from the primary analysis is overturned. The delta will increase in 10% increments (ie, 0%, 10%, 20%, etc) of the expected treatment difference of 3 points and/or the observed treatment difference between SEP-363856 and placebo from the primary analysis of MMRM model until the conclusion of the primary analysis is overturned. When delta = 0 it is MAR. When delta > 0 it is MNAR.

1) Using Monte Carlo Markov Chain (MCMC) methodology from PROC MI to impute the intermittent missing data to a monotone missing pattern.
2) Using a standard MAR-based multiple imputation approach from PROC MI to impute the monotone missingness data.
3) For subjects in the treated group and with a dropout reason of AE or LOE or subject withdrew consent, a delta will be added for all the values after the dropout time.
4) Using MMRM model in the primary analysis to analyze the completed data using PROC MIXED on the multiple imputed data.
5) Obtaining the overall results using PROC MIANALYZE.

9.4.1.2.1.2 Control Based Imputation Methods

For 2 scenarios:

1) Dropout reasons due to either AE or LOE or subject withdrew consent as MNAR
2) All dropouts as MNAR

The analysis method is similar to “standard” multiple imputations, except parameters for the imputation model obtained from only the placebo + ADT (control) group. Missing data for both the placebo + ADT and SEP-363856 + ADT groups are imputed based on the imputation model derived from data from the ADT + placebo group. If the drug improves outcomes prior to drop out, this benefit is carried into subsequent imputed values, but will diminish over time in accordance with the correlation structure.

In addition, model based MNAR methods such as the shared parameter model[50] and random coefficient pattern mixture model[48] will be also performed.

9.4.1.2.2 Sensitivity Analyses for Violation of Normality Assumption

The primary endpoint MMRM analysis is a maximum likelihood method that relies on normality assumption. Residual analyses will be carried out to examine model assumption.

In the case of gross violations of the normality assumptions, nonparametric van Elteren test[55] will be performed to compare treatment effect at Week 14 on the MI data. The van Elteren test is a generalized Cochran–Mantel–Haenszel procedure useful for stratified continuous data in nonnormal setting. It belongs to a general family of Mantel-Haenszel mean score tests. The test is performed via SAS procedure PROC FREQ, by including CMH2 and SCORES = MODRIDIT options in the TABLE statement. The stratification factor is trial center.

In addition, other methods that are robust to distributional assumption will also be performed to provide different views on the primary efficacy result, these include generalized estimating equations (GEE), weighted GEE (WGEE), and MI-robust regression.

For MI-van Elteren test and MI-robust regression, imputation datasets will be generated with SAS MI procedure, each dataset will be analyzed, then an overall estimate is derived with SAS MIANALYZE procedure.

9.4.1.3 Key Secondary Efficacy Endpoint Analysis

The secondary estimand has similar attributes to the primary estimand. The key secondary efficacy variable is the change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in CGI-S.

CCI



CCI

[redacted]

CCI

[redacted]

9.4.1.5 Control of Experiment-wise Type 1 Error

The overall type I error rate for the primary and key secondary endpoint will be maintained at 0.05. To control the overall experiment-wise type I error at 0.05 level, a fixed sequence testing approach will be applied. The statistical test will be performed in the following order:

(1) Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in MADRS total score.
(2) Change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in CGI-S.

The test for the subsequent hypothesis will be performed only if the test for the previous hypothesis is statistically significant.

CCI

[redacted]

9.4.2 Safety Analysis

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

The incidence of the following events will be summarized by treatment group:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

9.4.2.2 Clinical Laboratory Data

Clinical laboratory test data (observed and change from baseline data) and the incidence of potentially clinically relevant clinical laboratory tests will be summarized. Clinical laboratory test data will be presented in listings.

9.4.2.3 Physical Examination and Vital Signs Data

Physical examination data will be presented in a listing.

Vital signs data (observed and change from baseline data) and the incidence of potentially clinically relevant vital signs will be summarized. Vital sign data will be presented in a listing.

9.4.2.4 Electrocardiogram Data

Electrocardiogram data (observed and change from baseline data) and the incidence of potentially clinically relevant ECGs will be summarized. Electrocardiogram data will be presented in a listing.

9.4.2.5 Other Safety Data

9.4.2.5.1 Extrapyramidal Symptoms

Change from end of Phase A (Week 8 visit) in scores for the SAS, AIMS, and BARS will be evaluated using ANCOVA, with end of Phase A (Week 8 visit) value as covariate and treatment and, in analysis of LOCF dataset, trial center as main effects. Analyses of the OC dataset for these scales will not include trial center in the statistical model.

9.4.2.5.2 Sexual Function

Change from end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in scores for the CSFQ scale will be evaluated separately for male and female subjects using ANCOVA, with the end of Phase A (Week 8 visit) value as a covariate and treatment and trial site as main effects in analysis of the LOCF dataset. Analyses of the OC dataset for this scale will not include trial center in the statistical model.

9.4.2.5.3 Pittsburgh Sleep Quality Index

Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in PSQI will be evaluated using ANCOVA, with the end of Phase A (Week 8 visit) value as a covariate and treatment and trial site as main effects in analysis of the LOCF dataset. Analyses of the OC dataset for this scale will not include trial site in the statistical model.

9.4.2.5.4 Suicidality

Suicidality monitored during the trial using the C-SSRS will be summarized as the number and percentage of subjects reporting any suicidal behavior, ideation, behavior by type (4 types), ideation by type (5 types), and treatment-emergent suicidal behavior and ideation.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, sex at birth, weight, height, and body mass index for the randomized subjects will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

Baseline disease severity and psychiatric history will also be summarized by descriptive statistics for the Phase B Safety Analysis Set to identify any potential lack of balance between the treatment groups.

CCI



9.5.1 Data Monitoring Committee

An independent data monitoring committee (DMC) will be established and conduct periodic safety reviews of unblinded safety data. The details of the DMC structure and its roles and responsibilities will be documented in the DMC charter.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, Regulation (EU) No. 536/2014, applicable ICH GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the clinical trial sponsor. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eSource as well as IRE(s) and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the clinical trial sponsor and the investigator.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB/IEC that approves this protocol.

Each ICF will comply with the ICH GCP Guidelines, and local regulatory requirements. The investigator will ensure that the clinical trial sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB/IEC. In support of the site’s standard process for administering informed consent, this trial will also allow for electronic informed consent form (eICF) as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial subjects will be provided with controlled access to the eICF application by trial site staff. When the trial site staff and the subject agree that the subject has enough information to make an informed decision to participate, the subject will electronically sign in the eICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB/IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

CCI [redacted]

Trial sites in the US only: Signed consent will be collected at screening to perform the Duplicate Subject Check. Following the last contact with a subject, the duplicate enrollment system should be updated, as appropriate.

10.1.3 Recruitment Strategy

A subject recruitment plan may be developed and implemented to assist trial sites with their overall recruitment efforts for the trial.

10.1.4 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the clinical trial sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and clinical trial sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All trial intervention, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the clinical trial sponsor.

Subjects will be identified only by unique subject ID in eSource. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials, if necessary, subject to local regulations.

The contract between sponsor and trial sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Quality Control and Quality Assurance

10.1.5.1 Monitoring

The clinical trial sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the clinical trial sponsor's monitors will visit the trial sites during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.5.2 Auditing

The clinical trial sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, trial intervention supply, presence of required documents, the informed consent process, site operations, and delegation of authority and training, as applicable. The investigator will agree to cooperate and participate with audits.

Regulatory authorities may inspect the trial sites during or after the trial. The investigator will cooperate with such inspections and will contact the clinical trial sponsor immediately if such an inspection occurs.

10.1.6 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, trial intervention dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the clinical trial sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and clinical trial sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the clinical trial sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in eSource along with the start date and details of the deviation.

10.1.7 Records Management

10.1.7.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the eICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.7.2 Data Collection

During each subject's visit to the trial site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to trial intervention must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and trial intervention compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Source documents and source data will be captured electronically (where permitted by local regulation) in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated according to 21 Code of Federal Regulations Part 11. Changes to the data will be captured by an automatic audit trail.

Designated trial site staff will not be given access to the electronic source system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial sites for data collected directly into the application, rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified per the monitoring plan and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or their designee.

Another exception will be safety laboratory or central ECG data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

10.1.7.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with applicable ICH GCP guidance and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.7.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the clinical trial sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the clinical trial sponsor or (2) provision of an opportunity for the clinical trial sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the clinical trial sponsor. Such documentation is subject to inspection by the clinical trial sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a clinical trial sponsor-specified timeframe. Notice of such transfer will be given to the clinical trial sponsor in writing.

10.1.7.5 Dissemination of Clinical Trial Data

Clinical trial data will be released in accordance with required disclosure rules and regulations. For clinical trials registered on clinicaltrials.gov, results will be disclosed within 12 months of last patient, last visit (LPLV) unless other deferral requirements can be met at the time of required disclosure. In that case, the clinical trial results will be deferred the maximum amount of time of 2 years from the 12 month past LPLV. For clinical trials registered in the European Union, clinical trial results will be automatically deferred for disclosure up to the maximum amount of time allowed according to the phase and trial population of the clinical trial being conducted.

10.1.7.6 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial subjects who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial subjects consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed per the schedules of assessments (Table 1.3-1 and Table 1.3-2).

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Hematocrit Platelets Red blood cell count White blood cell count (absolute and differential) Urinalysis: Blood Glucose Ketones pH Protein Specific gravity Microscopic exam (performed only if any part of the urinalysis is not negative)	Serum Chemistry: Alkaline phosphatase Alanine aminotransferase Albumin Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol (total, low density lipoprotein, and high density lipoprotein) Creatine phosphokinase Creatinine C-reactive protein (high sensitivity assay) Gamma glutamyl transferase Glucose Inorganic phosphorous Insulin Lactate dehydrogenase Magnesium Potassium Sodium Triglycerides Total bilirubin Total protein Uric acid Additional Tests: Glycosylated hemoglobin Coagulation parameters (PT, aPTT, and INR) Prolactin[a] Thyroid stimulating hormone with reflex to thyroxine if thyroid stimulating hormone is abnormal Blood alcohol Urine drug screen (amphetamines, barbiturates, opiates, benzodiazepines, cocaine, THC, methadone, and phencyclidine) Urine pregnancy (POCBP only)

aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time.

[a]Laboratory results that could unblind the trial (eg, post-screening prolactin) will not be reported to trial sites or other blinded personnel until the trial has been unblinded.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Persons of childbearing potential are females at birth whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Persons of nonchildbearing potential do not meet definition of POCBP.

For sexually active subjects or POCBP, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remain abstinent) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP (females at birth) or 90 days after the last dose of IMP (males at birth). Unless the subject is sterile (ie, females at birth who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males at birth who have had a bilateral orchiectomy) or remains abstinent during the trial and for 30 days after the last dose of IMP (females at birth) or 90 days after the last dose of IMP (males at birth), 2 of the following clinical trial sponsor approved methods of birth control must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control injection, birth control implant, birth control patch, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in eSource. Subjects must also agree not to donate sperm from trial screening through 90 days after the last dose of IMP. Subjects with exclusively same-sex partners may not be required to practice birth control methods following discussion with the investigator and medical monitor.

Before enrolling subjects in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- ICF
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, subjects must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine pregnancy test for human chorionic gonadotropin (hCG) will be performed at the time points described in the schedules of assessments (Table 1.3-1 and Table 1.3-2). On suspicion of pregnancy, an unscheduled urine or serum pregnancy test may be performed. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all POCBP should be instructed to contact the investigator immediately if they suspect they or their partner might be pregnant (eg, missed or late menstrual cycle). If a subject is suspected to be pregnant before receiving IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the clinical trial sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 30 days after the last dose of IMP (females at birth) or 90 days after the last dose of IMP (males at birth), and record the event on the IRE form and forward it to the clinical trial sponsor. The clinical trial sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the clinical trial sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Protocol Amendments

The investigator will not make any changes to this protocol without the clinical trial sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the clinical trial sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the clinical trial sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The clinical trial sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the clinical trial sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

10.4.1 Protocol Amendment(s)/Administrative Change(s)

CCI

[redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

11 References

[1] Hopkins SC, Dedic N, Koblan KS. Effect of TAAR1/5-HT1A agonist SEP-363856 on REM sleep in humans. Transl Psychiatry. 2021;11(1):228.

[2] Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs. 2013;27(9):703-716.

[3] Gainetdinov RR, Hoener MC, Berry MD. Trace amines and their receptors. Pharmacol Rev. 2018;70(3):549-620.

[4] Friedrich MJ. Depression is the leading cause of disability around the world. JAMA. 2017;317(15):1517.

[5] Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry. 2018;75(4):336-346.

[6] Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289(23):3095-3105.

[7] Marcus M, Yasamy MT, van Ommeren M, Chisholm D, Saxena S. Depression: A global public health concern. World Health Organization. Available from: https://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf. Accessed 09 Dec 2021.

[8] Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry. 2015;76(2):155-162.

[9] Kraus C, Kadriu B, Lanzenberger R, Zarate CA, Kaspe S. Prognosis and improved outcomes in major depression: a review. Transl Psychiatry. 2019;9(1):127.

[10] Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry. 1999;156:1000-1006.

[11] American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. 4th ed; 2000.

[12] Eaton WW, Shao H, Nestadt G, Lee BH, Bienvenu OJ, Zandi P. Population-based study of first onset and chronicity in Major Depressive Disorder. Arch Gen Psychiatry. 2008;65:513-520.

[13] Rush JA. STAR*D: what have we learned? Am J Psychiatry. 2007;164(2):201-204.

[14] Moller HJ. Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. World J Biol Psychiatry. 2008;9(2):102-114.

[15] Mulder RT, Frampton CM, Luty SE, Joyce PR. Eighteen months of drug treatment for depression: predicting relapse and recovery. J Affect Disord. 2009;114(1-3):263-270.

[16] Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatr Clin North Am. 2002;25(4):685-698.

[17] McIntyre RS, O'Donovan C. The human cost of not achieving full remission in depression. Can J Psychiatry. 2004;49(Suppl 1):10S-16S.

[18] Sobocki P, Jonsson B, Angst J, Rehnberg C. Cost of depression in Europe. J Ment Health Policy Econ. 2006;9:87-98.

[19] Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults: III. Pharmacotherapy. J Affect Disord. 2009;117 Suppl 1:S26-S43.

[20] Borges S, Chen YF, Laughren TP, Temple R, Patel HD, David PA, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry. 2014;75(3):205-214.

[21] Sim K, Lau WK, Sim J, Sum MY, Baldessarini RJ. Prevention of relapse and recurrence in adults with major depressive disorder: systematic review and meta-analyses of controlled trials. Int J Neuropsychopharmacol. 2015;19(2):pyv076.

[22] APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts. American Psychological Association. https://www.apa.org/depression-guideline/guideline.pdf. Published Feb 2019. Accessed 16 Oct 2024.

[23] Sunovion Pharmaceuticals Inc. SEP-363856 Investigator's Brochure, Version 11.0. Release date, 07 Dec 2021.

[24] Sunovion Pharmaceuticals Inc. SEP-363856 Addendum No. 1 to Investigator's Brochure (Major Depressive Disorder), Version 1.0.

[25] Bahar MA, Kamp J, Borgsteede SD, Hak Eelo, Wilffert B. The impact of CYP2D6 mediated drug-drug interaction: a systematic review on a combination of metoprolol and paroxetine/fluoxetine. Br J Clin Pharmacol. 2018;84(12):2704-2715.

[26] Mikami A, Ohtani H, Hori S, Sawada Y. Pharmacokinetic model incorporating mechanism-based inactivation of CYP2D6 can explain both non-linear kinetics and drug interactions of paroxetine. Int J Clin Pharmacol Ther. 2013;51(5):374-382.

[27] Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2008;27(1):31-40.

[28] US Food and Drug Administration (homepage on the Internet). Rockville, MD: FDA Public Health Advisory 19 Jul 2006 (cited 24 Oct 2011). Available at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationf.

[29] US Food and Drug Administration (homepage on the Internet). Rockville, MD: FDA Drug Safety Communication 26 Jul 2011 (updated 21 Oct 2011; cited 24 Oct 2011). Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts

[30] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.

[31] Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry. 2008;192:52-58.

[32] Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publication No. ADM 76-338). Rockville, MD, US Department of Health, Education, and Welfare, 1976:218-222.

[33] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50-55.

[34] Hamilton M. The diagnosis and rating of anxiety. In: Lader MH, editor. Studies of Anxiety. Kent, UK: Br J Psychiatry Spec Publ; 1969:76-79.

[35] Hamilton M. Hamilton anxiety scale. In: Guy W, editor. ECDEU assessment manual for psychopharmacology (revised). Rockville, MD: US Department of Health, Education, and Welfare; 1976:193-198.

[36] Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry. 2008;192(1):52-58.

[37] Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278-296.

[38] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;22:56-62.

[39] Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry. 1988;45:742-747.

[40] Simpson GN, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand. 1970;212(Suppl 44):S11-S19.

[41] Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publication No. ADM 76-338). Rockville, MD, US Department of Health, Education, and Welfare, 1976:218-222.

[42] Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-676.

[43] Keller A, McGarvey EL, Clayton, AH. Reliability and construct validity of the changes in sexual functioning questionnaire short-form (CSFQ-14), J Sex Marital Ther, 2006;32(1):43-52.

[44] Siddiqui O, Hung JHM, O'Neill R. MMRM vs. LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat. 2009;19(2):227-46.

[45] Diggle P, Kenward MG. Informative drop-out in longitudinal data analysis. Applied Statistics. 1994;43(1):49-93.

[46] Little RJA. Pattern-mixture models for multivariate incomplete data. J Am Stat Assoc. 1993;88(421):125-134.

[47] Little RJA. Modeling the drop-out mechanism in repeated measures studies. J Am Stat Assoc. 1995;90(431):1112-1121.

[48] Hedeker D, Gibbons RD. Application of random effects pattern-mixture models for missing data in longitudinal studies. Psychological Methods. 1997;2(1):64-78.

[49] Ali MW, Siddiqui O. Multiple imputation compared with some informative dropout procedures in the estimation and comparison of rates of change in longitudinal clinical trials with dropouts. J Biopharm Stat. 2000;10(2):165-181.

[50] Wu MC, Bailey KR. Estimation and comparison of changes in the presence of informative right censoring: conditional linear model. Biometrics. 1989;45(3):939-955.

[51] Hobart M. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of the safety and efficacy of fixed-dose brexpiprazole (OPC-34712) as adjunctive therapy in the treatment of adults with major depressive disorder with and without anxious distress. Otsuka Clinical Study Report for Protocol 331-13-214, issued 14 Oct 2016.

[52] Skuban A. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of the safety and efficacy of two fixed-doses of OPC-34712 as adjunctive therapy in the treatment of adults with major depressive disorder, the Polaris trial. Otsuka Clinical Study Report for Protocol 331-10-227, issued 04 Jun 2014.

[53] Youakim JM. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of the safety and efficacy of fixed-dose OPC-34712 as adjunctive therapy in the treatment of adults with major depressive disorder, the Pyxis Trial. Otsuka Clinical Study Report for Protocol 331-10-228, issued 18 Sep 2013.

[54] Hobart M. A phase 3, multicenter, randomized, double-blind, placebo- and active comparator-controlled trial of flexible-dose brexpiprazole (OPC-34712) as adjunctive therapy in the treatment of adults with major depressive disorder, the Delphinus trial. Otsuka Clinical Study Report for Protocol 331-12-282, issued 22 Mar 2017.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the clinical trial sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, SEP-363856, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the institutional review board (IRB) or receive a favorable opinion by the independent ethics committee (IEC) responsible for such matters in the clinical trial facility where SEP-363856 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the clinical trial sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB/IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the clinical trial sponsor. I agree that clinical data entered in eSource by me and my staff will be utilized by the clinical trial sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow clinical trial sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the clinical trial sponsor any adverse experiences in accordance with the terms of the clinical trial sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the clinical trial sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: Protocol 382-201-00001 Amendment 5

Document Number: 1000179489

Signed by	Meaning of Signature	Server Date (GMT) dd-MM-yyyy hh:mm:ss
PPD	Clinical Approval	22-Jul-2025 20:02:06
PPD	Clinical Pharmacology Approval	23-Jul-2025 01:15:14
PPD	Biostatistics Approval	23-Jul-2025 14:01:45