Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder

NCT Number: NCT02371980

Protocol Approve Date: 25 September 2015

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL AMENDMENT

A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder

Vortioxetine, 5, 10, and 20 mg, Relapse Prevention Study in Adults with Major Depressive Disorder

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015		
Study Number:	LuAA21004_402		
IND Number:	76,307	**EudraCT Number:**	N/A
Compound:	Vortioxetine		
Date:	25 September 2015	Amendment Number:	01

Date	Amendment Number	Region
23 October 2014	Initial Protocol	North America (United States)
25 September 2015	Amendment 01	North America (United States)

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America (United States) Contact
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and/or package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment No. 1 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 1.

The primary purpose of this amendment is to update the protocol regarding exclusion criteria #12 and the addition of exclusion criteria #24, the addition of using Clinical Trial Subject Database, and the addition of PK and RNA blood sampling for any open-label withdrawal visit. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in Appendix F. The following is a summary of the changes made in the amendment:

1. Clarification of exclusion criteria #12 for unstable illnesses.

   Justification: To exclude subjects with fibromyalgia, obstructive sleep apnea, chronic pain diagnosis, and morbid obesity due to the potential impact on assessment of the primary endpoint.

2. Addition of exclusion criteria #24 excluding subjects who are treatment- resistant.

   Justification: To clarify the exclusion of those subjects who are considered to be treatment-resistant as defined by not responding to adequate monotherapy treatments of at least 6 weeks duration or only responding to combination or augmentation therapy.

3. Addition of utililizing Clinical Trial Subject Database (CTSdatabase).

   Justification: To include the use of a subject registry to help reduce subjects from enrolling into multiple clinical trials simultaneously by identifying duplicate subjects before enrollment.

4. Addition of PK and RNA blood sampling for any open-label withdrawal visit.

   Justification: To clarify the PK and RNA blood sample procedure for subjects who withdraw during the open-label period.

5. Clarification for rater qualifications for Clinical Global Improvement (CGI).

   Justification: To allow for flexibility for a competent rater who is not a physician (MD) or doctor of osteopathy (DO) to qualify to rate this scale with sponsor approval.

6. Addition of a Relapse Checklist to be completed at Visits 18 to 48.

   Justification: To provide a tool for sites to use to evaluate potential indicators of relapse for each subject at each visit post baseline during the double blind-period.

7. Correction of serious adverse event (SAE) language.

   Justification: This wording was changed to be consistent with ICH and other guidance documentation.

8. Correction of inconsistencies within the original protocol.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** Vortioxetine	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder	**IND No.:** 76,307	**EudraCT No.:** N/A
Study Number: LuAA21004_402	**Phase:** 4	

Study Design:

This study is a randomized, double-blind, placebo-controlled, phase 4 study to evaluate 3 fixed doses (5, 10, and 20 mg oral tablets) of vortioxetine once daily in the prevention of relapse in adult subjects with major depressive disorder (MDD) who have responded to acute treatment with vortioxetine.

This study is comprised of a 16-week open-label treatment period followed by a 32-week double-blind randomized treatment periods. This study will enroll approximately 1100 subjects into the open label in order to target approximately 600 subjects into the double-blind treatment phases and will be conducted at approximately 60 sites in the United States.

Eligible subjects are men and women between the ages of 18 and 75, inclusive, meeting the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for recurrent MDD, who have had at least 2 major depressive episodes prior to the current episode, with a current episode of between 8 weeks and 18 months duration from screening, and a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≥26. At Baseline I (open-label baseline),eligible subjects will be enrolled into the 16-week open-label treatment period and will receive 10 mg vortioxetine.

Subjects who are in response (defined as a ≥50% reduction in MADRS total score from Baseline I) at Week 8 will continue for an additional 8 weeks of treatment (Stabilization period) and will continue to receive 10 mg vortioxetine. Subjects must continue to meet response criteria as assessed at every study visit during the Stabilization period. In addition, subjects must meet remission criteria (defined as ≤12 MADRS total score) at weeks 14 and 16 to be eligible for randomization into the double-blind treatment period. Subjects who do not meet the response and/or remission criteria will be withdrawn from the study and will complete an early withdrawal visit.

At Baseline II (double-blind randomization), subjects who have met the randomization criteria (response and remission as described above) and have not met any other withdrawal criteria will be randomized in a ratio of 1:1:1:1 of the following 4 treatment groups for 32 weeks of double-blind treatment: vortioxetine 5 mg; vortioxetine 10 mg; vortioxetine 20 mg; and placebo.

Subjects will be seen twice the first month and then once monthly during the remainder of the 32-week double-blind treatment period. Subject well-being calls will be made every 2 weeks after Week 20, in between scheduled subject visits.

Subjects will be considered as "relapsed" and withdrawn from the study if the following criteria are met: MADRS ≥22, or lack of efficacy as determined by the investigator. In addition, investigator judgment should be used to determine unsatisfactory treatment response indicative of relapse to depression, such as subject hospitalization for depression, medication prescribed for MDD, electroconvulsive therapy, suicide attempt, etc.

Primary Objectives:

To determine the efficacy of vortioxetine (5, 10, and 20 mg) versus placebo during the first 28 weeks of the 32-week double-blind treatment period in the prevention of relapse in subjects with MDD who responded to acute treatment with vortioxetine 10 mg.

Secondary Objective:

To determine the overall efficacy of vortioxetine versus placebo during continuation treatment of subjects with MDD.

Safety Objective:

To evaluate long-term safety and tolerability of vortioxetine versus placebo in subjects with MDD.

Additional Objectives:

- To assess the effect of long-term treatment with vortioxetine and placebo on suicidal ideation and behavior.
- Determine the pharmacokinetic parameters of vortioxetine using a population pharmacokinetic approach.
- Samples for pharmacogenomics will be collected and stored for possible exploratory investigation of drug response or disease. Pharmacogenomics analyses may be conducted to explore relationships of gene polymorphisms with drug responses, as indicated by the findings.

Subject Population: Male or female **s**ubjects with recurrent MDD aged 18-75 years, inclusive.

Number of Subjects:	**Number of Sites:**
Estimated total in the open-label lead-in phase in order to meet the target for the double-blind phase: Approximately 1100 subjects Estimated total in the double-blind phase: Approximately 600 subjects Per treatment group in the double-blind phase: 150 subjects	Approximately 60 sites in United States
Dose Level(s):	**Route of Administration:**
5 mg vortioxetine 10 mg vortioxetine 20 mg vortioxetine Placebo	Oral
Duration of Treatment:	**Period of Evaluation:**
Up to 48 weeks	Up to 55 weeks

Main Criteria for Inclusion:

- The subject suffers from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x), and the current episode is confirmed by the Mini International Neuropsychiatric Interview (MINI), hereafter referred to as MINI.
- The reported duration of the current episode is ≥8 weeks and ≤18months.
- The subject had at least 2 other major depressive episodes (MDE) before the current episode.
- The subject has a MADRS total score ≥26 at the Screening and Baseline I Visits.
- The subject is a man or woman aged 18 to 75 years, inclusive.

Main Criteria for Exclusion:.

- The subject has participated in 2 or more clinical studies in the year prior to Screening, or has participated in a clinical trial for a psychiatric condition that is exclusionary per this protocol.
- The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
- The subject has one or more of the following:
  a) Any current psychiatric disorder which is the primary focus of treatment other than MDD as defined in the DSM-IV-TR, and assessed by the MINI.
  b) Current or history of: manic or hypomanic episode, schizophrenia or any other psychotic disorder, including schizoaffective disorder, major depression with psychotic features, bipolar depression with psychotic features, obsessive compulsive disorder (OCD), mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR.
  c) Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) as defined in the DSM-IV-TR that has not been in full and sustained remission for at least 3 months from the day of screening (Subject must also have negative urine drug screen at Screening and Baseline I.)
  d) Presence or history of a clinically significant neurological disorder (including epilepsy) as determined by the investigator.
  e) Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc).
  f) Any Axis II disorder as defined by DSM-IV-TR that might compromise the study.
- The current depressive symptoms of the subject are considered by the investigator to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each.
- The subject has a history of lack of response to previous adequate treatment with vortioxetine for any MDD episode with adequate treatment considered to be known dose of vortioxetine in the approved recommended dose range for at least 6 weeks duration.
- The subject has received electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial magnetic stimulation within 6 months prior to Screening.
- The subject has started receiving formal cognitive or behavioral therapy, systematic psychotherapy within 30 days from screening or plans to initiate such therapy during the study (supportive therapy, marital therapy and bereavement counseling are allowed).
- The subject has a significant risk of suicide according to the investigator's clinical judgment or has a score ≥5 on item 10 (suicidal thoughts) of the MADRS or has made a suicide attempt in the previous 6 months.
- The subject has a clinically significant unstable illness, for example hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, hematological, infectious, dermatological disorder or metabolic disturbance.
- The subject has a known history of or currently has increased intraocular pressure or is at risk of acute narrow-angle glaucoma.
- The subject has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or efficacy.

Randomization Criteria:

- The subject is in response from the Week 8 Visit through Week 16 Visit (response defined as a ≥50% reduction in MADRS total score from Baseline I).

- The subject is in remission (MADRS total score ≤12) at the Week 14 and Week 16 visits.
- The subject has not met any other withdrawal criteria, such as major protocol violation.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

The primary endpoint is time from randomization to relapse during the first 28 weeks of the 32-week double-blind treatment period with relapse defined as depression (MADRS ≥22), or lack of efficacy as determined by the investigator.

Secondary Endpoints:

- Change from double-blind baseline in MADRS total score at all time points assessed.
- Change from double-blind baseline in Clinical Global Impression Scale-Severity of Illness Scale (CGI-S) score at all time points assessed.
- Clinical Global Impression Scale-Global Improvement Scale (CGI-I) score at all time points assessed.
- Time from randomization to relapse during the entire 32-week double-blind treatment period with relapse defined as depression (MADRS ≥22), or lack of efficacy as determined by the investigator.

Safety Assessments:

Safety and tolerability of vortioxetine will also be evaluated using the following general assessments:

- Adverse events (AEs).
- Laboratory values.
- Vital signs.
- Weight.
- Electrocardiograms (ECGs).

Additional Endpoints:

- The time from randomization to withdrawal for any reason during 28 weeks of double-blind treatment.
- Columbia-Suicide Severity Rating Scale (C-SSRS) summary data at all time points assessed.
- Estimate individual exposure parameters of vortioxetine, including area under the plasma concentration-time curve from time 0 to time tau (AUC_{τ}), average serum concentration (C_{av}), maximum observed plasma concentration (C_{max}).

Statistical Considerations:

Primary Efficacy Analysis:

The primary efficacy variable will be the time from randomization to relapse during the first 28 weeks of the 32-week double-blind treatment (date of relapse – date of randomization +1), with relapse defined as depression (MADRS ≥22), or lack of efficacy as determined by the investigator. Primary analysis will be based on a Cox model with an exact method to handle ties (based on the full analysis set [FAS]), with treatment as the factor and baseline MADRS total score as the covariate of the Cox model.

Secondary Efficacy Analysis:

Change from double-blind Baseline II in MADRS total score will be analyzed using a mixed model for repeated measurements (MMRM) analysis with treatment, center, week, treatment-by-week interaction, baseline MADRS total score-by-week as fixed effects, and a completely unstructured covariance matrix. Change in MADRS total score will also be analyzed using analysis of covariance (ANCOVA), with treatment and center as fixed factors, Baseline II MADRS total score as covariate, and using the last-observation-carried forward (LOCF) technique and observed case (OC) methods. Comparisons between the different doses of vortioxetine and placebo will be performed over all the assessment points.

CGI-I scores and change from Baseline II in the CGI-S will be analyzed by study visit using both MMRM and

ANCOVA similar to the ones described above for the change of MADRS total score.

Time from randomization to relapse of MDD occurring during the entire 32-week double-blind treatment period will be analyzed using a Cox model similar to the one described above for the primary variable.

Controlling Type I Error

To control the type I error of the study, comparison between each dose of vortioxetine and placebo will be tested in the sequential order of 20 mg vs placebo, 10 mg vs placebo, and 5 mg vs placebo at significance level 0.05; as soon as a dose is non-significant from placebo at 0.05, the testing procedure stops for all subsequent dose(s).

Safety Analysis

The safety data will be summarized for the open-label period and double-blind period separately.

Adverse Events

Adverse events will be reported throughout the study. The definition of treatment-emergent adverse events will be provided in the statistical analysis plan (SAP). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term. Adverse events that were reported more than once by a subject during the same period will be counted only once for that subject and at period of the maximum severity.

Clinical Evaluations

Absolute values and changes from Screening/Baseline I in clinical safety laboratory tests, vital signs, ECG parameters, and weight/body mass index will be summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated.

Sample Size Justification: Assuming a cumulative relapse rate at 28 weeks of 15% for the vortioxetine group versus 30% for the placebo group, a total of 600 subjects (150 per treatment group) will provide 85% power to find a statistically significant difference between each dose of vortioxetine and placebo at a 5% significance level.

It is anticipated that approximately 55% of the patients enrolled into the open-label period will qualify for the double-blind study phase. Therefore, a total of about 1100 patients will need to be enrolled into the open-label period of the study. However, if the number of subjects who relapsed during the double-blind treatment period is much less than expected, sample size adjustment will be considered. In addition, as the required number of subjects enrolled into the open-label period is dependent upon the number randomized into the double-blind, the number enrolled may be more or less than the estimated 1100.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
APA	American Psychiatric Association
AST	aspartate aminotransferase
AUC_{τ}	area under the plasma concentration-time curve from time 0 to time tau
bpm	beats per minute
C_{av}	average serum concentration
CGI-I	Clinical Global Impression Scale – Global Improvement Scale
CGI-S	Clinical Global Impression Scale – Severity of Illness Scale
C_{max}	maximum observed plasma/blood/serum concentration
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTSdatabase	Clinical Trial Subject Database (CTSdatabase)
DNA	deoxyribonucleic acid
DO	doctor of osteopathy
DRESS	drug reaction with eosinophilia and systemic symptoms
DSM-IV-TR	Diagnostic & Statistical Manual of Mental Disorders, 4th Edition - Text Revision
DVD	digital versatile disc
DvX	diagnostic validation
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IR	immediate release
IRB	institutional review board
IWRS	interactive web response system
K2EDTA	potassium ethylenediaminetetraacetic acid

LFT	liver function tests
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episodes
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
NONMEM	nonlinear mixed effect modeling
OC	observed case
OCD	obsessive compulsive disorder
OE	over encapsulation
PI	principal investigator
PK	Pharmacokinetic(s)
PPS	per protocol set
PTE	pretreatment event
QD	once daily
OE	overencapsulation
QTc	corrected QT interval
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SIGMA	Structured Interview Guide for the MADRS
SJS	Stevens-Johnson syndrome
SUSAR	suspected unexpected serious adverse reaction
TEN	toxic epidermal necrolysis
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

The prevalence of major depressive disorder (MDD) in the United States is 8.3%, based on a recent World Health Organization (WHO) World Mental Health survey [1]. Furthermore, the burden is likely to grow over the coming years. According to the WHO, depression alone accounts for 4.3% of the global burden of disease and is among the largest single causes of disability worldwide (11 % of all years lived with disability globally), particularly for women [2].

Depression poses an economic burden both on the patients, their families and friends, and on society. The ability of the depressed patients or their caregivers to work and make productive contributions to the economy is reduced, whereas the utilization of treatment and support services is increased. The economic consequences of these health losses are significant: a recent study estimated that the cumulative global impact of mental disorders in terms of lost economic output will amount to US$ 16.3 million between 2011 and 2030 [2].

Depression is recurrent in 75% to 80% of patients, becomes chronic (that is, lasts 2 years or longer) in 15% to 20% of depressed patients [3,4], and can lead to substantial impairments in an individual's ability to take care of his/her everyday responsibilities. Furthermore, depression may lead to suicide, and of those patients who are treated for depression, approximately 15% commit suicide [5].

The risk of relapse of recurrence, chronicity (as measured by the duration of episodes) and treatment resistance increases with each new episode. Thus, treatment to full remission and continue treatment to prevent relapse and recurrence are both major priorities for management of recurrent MDD [6].

Clinical practice guidelines, such as those provided by the American Psychiatric Association (APA), recommend that patients who respond to acute-phase therapy with antidepressant medications receive at least 6 months of continuation therapy to prevent relapse [7].

Vortioxetine (LuAA21004) is an antidepressant agent approved in 2013 in the United States and the European Union for treatment of MDD. It differs from preexisting antidepressants in that it combines 2 pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter. Vortioxetine is an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors, and an inhibitor of the 5-HT transporter [8,9].

During the clinical development program, the efficacy, safety and tolerability of vortioxetine in MDD subjects was evaluated at doses from 1 to 20 mg/day in short-term efficacy studies of 6-8 weeks duration and long-term safety studies up to 52 weeks duration. Vortioxetine was safe and well-tolerated across the dose range. The efficacy of vortioxetine in the treatment of MDD was established in six 6-8 week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly). Efficacy was established at doses of 5, 10, 15 and 20 mg with the recommended starting dose being 10 mg/day [10].

The long-term efficacy and maintenance of effect of vortioxetine treatment at doses of 5 and 10 mg/day has been previously established in subjects with MDD [11]. The aim of this study is to evaluate the efficacy of vortioxetine at 5 and 10 mg/day as well as the highest approved dose of vortioxetine 20 mg/day in the prevention of relapse in patients with MDD.

4.2 Rationale for the Proposed Study

MDD is a long-term illness for many patients and maintenance therapy is recommended to prevent relapse in patients with recurrent depression. This study is being conducted to evaluate the long-term maintenance of subjects treated with vortioxetine in the prevention of relapse. Vortioxetine doses of 5, 10, and 20 mg are being explored in this randomized withdrawal study. The primary endpoint will be assessed during the first 28 weeks of the 32-week double-blind treatment period to allow sufficient time to detect a difference in the time to relapse between vortioxetine and placebo.

Blood samples for pharmacogenomic assessment are being collected in this study. Pharmacogenomic analysis may be conducted to investigate the contribution of genetic variance on drug response, eg, its efficacy and safety. Participation of study subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research on banked samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to evaluate the efficacy of vortioxetine (5, 10, and 20 mg) versus placebo during the first 28 weeks of the 32-week double-blind treatment period in the prevention of relapse in subjects with (MDD) who responded to acute treatment with vortioxetine 10 mg.

5.1.2 Secondary Objective

To evaluate the overall efficacy of vortioxetine versus placebo during continuation treatment of subjects with MDD

5.1.3 Safety Objective

To evaluate long-term safety and tolerability of vortioxetine versus placebo in subjects with MDD

5.1.4 Additional Objectives

- To assess the effect of long-term treatment with vortioxetine and placebo on suicidal ideation and behavior.
- Determine the pharmacokinetic (PK) parameters of vortioxetine using a population pharmacokinetic approach.
- Samples for pharmacogenomics will be collected and stored for possible exploratory investigation of drug response or disease. Pharmacogenomics analyses may be conducted to explore gene polymorphism relationships with drug responses, as indicated by the findings.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is time from randomization to relapse during the first 28 weeks of the 32-week double-blind treatment with relapse defined as depression Montgomery-Asberg Depression Rating Scale (MADRS ≥22), or lack of efficacy as determined by the investigator.

5.2.2 Secondary Endpoints

- Change from double-blind baseline in MADRS total score at all time points assessed.
- Change from double-blind baseline in Clinical Global Impression Scale – Severity of Illness (CGI-S) score at all time points assessed.
- Clinical Global Impression Scale – Global Improvement Scale (CGI-I) score at all time points assessed.

- Time from randomization to relapse during the entire 32-week double-blind treatment period with relapse defined as depression (MADRS ≥22), or lack of efficacy as determined by the investigator.

5.2.3 Safety Assessments

Safety and tolerability of vortioxetine will also be evaluated using the following general assessments:

- Adverse events (AEs).
- Laboratory values.
- Vital signs.
- Weight.
- Electrocardiograms (ECGs).

5.2.4 Additional Endpoints

- The time from randomization to withdrawal for any reason during 28 weeks of double-blind treatment.
- Columbia-Suicide Severity Rating Scale (C-SSRS) summary data at all time points assessed.
- Estimate individual exposure parameters of vortioxetine, including area under the plasma concentration-time curve from time 0 to time tau (AUC_{τ}), average serum concentration (C_{av}), maximum observed plasma concentration (C_{max}).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This study is a randomized, double-blind, placebo-controlled, Phase 4 study to evaluate 3 fixed doses (5, 10, and 20 mg oral tablets) of vortioxetine once daily in the prevention of relapse in adult subjects with MDD who have responded to acute treatment with vortioxetine.

This study is comprised of a 16-week open-label treatment period followed by a 32-week double-blind randomized treatment periods. This study will enroll approximately 1100 subjects into the open-label phase in order to target approximately 600 subjects into the double-blind treatment phases and will be conducted at approximately 60 sites in the United States.

Men and women between the ages of 18 and 75, inclusive, meeting the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for recurrent MDD, who have had at least 2 major depressive episodes (MDEs) prior to the current episode, with a current episode of between 8 weeks and 18 months duration from screening, a MADRS total score of ≥26, and who sign the informed consent form will be further assessed for study eligibility at a screening visit. At Baseline I, subjects who continue to meet all inclusion criteria and none of the exclusion criteria will be enrolled into a 16-week open-label treatment period. During the open-label period all subjects will receive 10 mg vortioxetine. Subjects will take their first dose of study medication the morning after their Baseline I visit. During the open-label treatment period, subjects will be seen every 2 weeks until randomization (Baseline II).

Subjects who are in response (defined as a ≥50% reduction in MADRS total score from Baseline I) at Week 8 will continue for an additional 8 weeks of treatment (Stabilization period) and will continue to receive 10 mg vortioxetine. Subjects must continue to meet response criteria as assessed at every study visit during the Stabilization period. In addition, subjects must meet remission criteria (defined as ≤12 MADRS total score) at weeks 14 and 16 to be eligible for randomization into the double-blind treatment period. Subjects who do not meet the response and/or remission criteria will be withdrawn from the study and will complete an early withdrawal visit. Subjects are to remain on 10 mg throughout the open-label period. If a subject requires a dose-adjustment, they should be withdrawn from study.

At Baseline II, subjects who have met the randomization criteria (response and remission as described above) and have not met any other withdrawal criteria will be randomized in a ratio of 1:1:1:1 of the following 4 treatment groups for 32 weeks of double-blind treatment: vortioxetine 5 mg; vortioxetine 10 mg; vortioxetine 20 mg; and placebo.

Subjects will be seen twice the first month and then once monthly during the remainder of the 32-week double-blind treatment period. Subject well-being calls will be made every 2 weeks after Week 20, in between scheduled subject visits.

Subjects will be considered as "relapsed" and withdrawn from the study if the following criteria are met: MADRS ≥22, or lack of efficacy as determined by the investigator. In addition, investigator judgment should be used to determine unsatisfactory treatment response indicative of

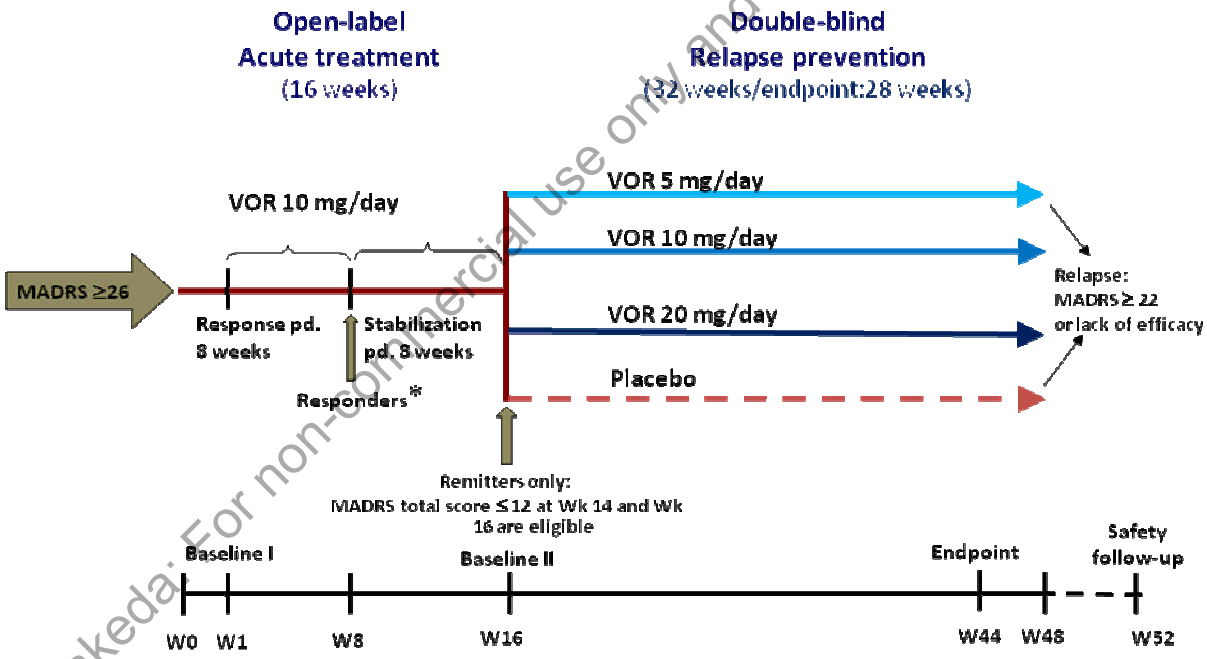
relapse to depression, such as subject hospitalization for depression, medication prescribed for MDD, electroconvulsive therapy, suicide attempt, etc.

A safety follow-up phone call will be made 30 days after completion of double-blind treatment. Subjects (either in open-label or double-blind) who discontinue or who are withdrawn prior to study completion will come to the site for an early withdrawal visit as soon as possible and will be contacted for a safety follow-up 30 days after the last dose of study medication.

NOTE: The investigators will be requested to make a note of the approximate date of relapse within the period since last visit rather than specify the visit at which relapse was detected. If necessary, subjects that are suspected of relapse or impending relapse (eg, clinically relevant worsening of depression symptoms) should come to the study site as soon as possible to be assessed.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



*Defined as ≥ 50% reduction in MADRS total score. Subjects must remain in response throughout stabilization period.

VOR = vortioxetine, pd. = period

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

Due to the character of the disorder, long-term studies are necessary to demonstrate that the short-term effect is maintained during an episode. As recommended in Food and Drug Administration (FDA) Guidance for Industry [12], a randomized withdrawal study is the most appropriate design to utilize in order to evaluate the maintenance of treatment effect.

6.2.2 Dose

The previously conducted long-term relapse prevention study evaluated vortioxetine at 5 and 10 mg/day [11]. As the approved dose range is 5 to 20 mg, this study will evaluate doses of vortioxetine at 5 and 10 mg/day as well as the highest dose of vortioxetine 20 mg/day.

6.2.3 Endpoints

The MADRS was selected for evaluation of the efficacy endpoints. The MADRS is a well-established tool for assessing the severity of depression symptoms [13,14].

The CGI-S, and CGI-I are used as secondary efficacy measures, since these scales are also frequently used to assess clinical response [15].

Adequate measures have been taken regarding the methodology of this study to assess suicidal risk. The selection criteria exclude the participation of subjects at significant risk for suicide. Throughout the study, signs of suicidal risk will be assessed both by rating scale assessment and by investigator's clinical judgment. Subjects will be withdrawn from the study in case of such risk. Furthermore, subjects will be screened for the history of suicidal behavior.

In order to more accurately and systematically assess the potential relationship between antidepressant agents and suicidality, the C-SSRS will be implemented in this study [16,17].

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk /benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrollment or first dose of study medication.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject suffers from recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x), and the current episode is confirmed by the Mini International Neuropsychiatric Interview (MINI).
4. The reported duration of the current episode is ≥8 weeks and ≤18months.
5. The subject had at least 2 other MDEs before the current episode.
6. The subject has a MADRS total score ≥26 at the Screening and Baseline I visits.
7. The subject is a man or woman aged 18 to 75 years, inclusive.
8. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use adequate contraception from signing of the informed consent throughout the duration of the study and for 30 days after the last dose.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.14 Pregnancy.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to screening or 5 half-lives prior to screening, whichever is longer.
2. The subject has previously or is currently participating in this study.
3. The subject has participated in 2 or more clinical studies in the year prior to screening, or has participated in a clinical trial for a psychiatric condition that is exclusionary per this protocol.
4. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

5. The subject has one or more of the following:
   a) Any current psychiatric disorder which is the primary focus of treatment other than MDD as defined in the DSM-IV-TR, and assessed by the MINI.
   b) Current or history of: manic or hypomanic episode, schizophrenia or any other psychotic disorder, including schizoaffective disorder, major depression with psychotic features, bipolar depression with psychotic features, obsessive compulsive disorder (OCD), mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR.
   c) Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) as defined in the DSM-IV-TR that has not been in full and sustained remission for at least 3 months from the day of screening (Subject must also have negative urine drug screen at Screening and Baseline I.)
   d) Presence or history of a clinically significant neurological disorder (including epilepsy) as determined by the investigator.
   e) Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc).
   f) Any Axis II disorder as defined by DSM-IV-TR that might compromise the study.
6. The current depressive symptoms of the subject are considered by the investigator to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each.
7. The subject has a history of lack of response to previous adequate treatment with vortioxetine for any MDD episode with adequate treatment considered to be known dose of vortioxetine in the approved recommended dose range for at least 6 weeks duration.
8. The subject has received electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial magnetic stimulation within 6 months prior to Screening.
9. The subject has started receiving formal cognitive or behavioral therapy, systematic psychotherapy within 30 days from screening or plans to initiate such therapy during the study (supportive therapy, marital therapy and bereavement counseling are allowed).
10. The subject has a significant risk of suicide according to the investigator's clinical judgment or has a score ≥5 on item 10 (suicidal thoughts) of the MADRS or has made a suicide attempt in the previous 6 months.
11. The subject is required to take excluded medications or it is anticipated that the subject will require treatment with at least 1 of the disallowed concomitant medications during the study.
12. The subject has a clinically significant unstable illness, for example hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, hematological, infectious, dermatological disorder or metabolic disturbance.

NOTE: For the purposes of this protocol fibromyalgia, obstructive sleep apnea, chronic pain diagnosis, and morbid obesity (BMI of ≥ 40) are considered unstable due to the potential impact on assessment of the primary endpoint.

13. The subject has a known history of or currently has increased intraocular pressure or is at risk of acute narrow-angle glaucoma.
14. The subject has 1 or more laboratory value outside the normal range, based on the blood or urine samples taken at the Screening Visit, that are considered by the investigator to be clinically significant; or the subject has any of the following values at the Screening Visit:
    a) A serum creatinine value >1.5 times the upper limits of normal (ULN).
    b) A serum total bilirubin value >1.5 xULN.
    c) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 xULN.
15. The subject has glycosylated hemoglobin (HbA1C)≥7% at screening and no prior diagnosis of diabetes and/or treatment for diabetes. NOTE: Subjects with known stable diabetes are not excluded.
16. The subject has a thyroid stimulating hormone (TSH) value outside the normal range at the Screening Visit that is deemed clinically significant by the investigator. NOTE: Free T4 will be checked if TSH is out of range. If free T4 is abnormal the subject will be excluded.
17. The subject has clinically significant abnormal vital signs as determined by the investigator.
18. The subject has an abnormal ECG as determined by the central reader and confirmed as clinically significant by the investigator.
19. The subject is positive for Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, or has a history of human immunodeficiency virus (HIV) infection.
20. The subject has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or efficacy.
21. The subject, in the opinion of the investigator, is unlikely to comply with the clinical study protocol or is unsuitable for any reason.
22. The subject has a history of hypersensitivity or allergies to vortioxetine.
23. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
24. The subject is considered to be treatment resistant, eg, the subject has not responded to adequate monotherapy treatments of at least 6 weeks' duration, or has only responded to combination or augmentation therapy.

7.3 Randomization Criteria

1. The subject is in response from the Week 8 Visit through Week 16 Visit (response defined as a ≥50% reduction in MADRS total score from Baseline I).
2. The subject is in remission (MADRS total score ≤12) at the Weeks 14 and 16 visits.
3. The subject has not met any other withdrawal criteria, such as major protocol violation.

7.4 Excluded Medications, Procedures, and Treatments

Use of any investigational medications will be prohibited within 30 days prior to Screening or 5 half-lives prior to Screening, whichever is longer.

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Table 7.a provides a list of excluded medications. Items with an 'X' indicate restrictions on either chronic use, or episodic use. Drug classes without an 'X' in these columns indicate no restrictions.

Table 7.a Excluded Medications and Treatments

Drug Class		Disallowed Prior to Baseline I unless otherwise noted	Disallowed (X) During the Study [sections without (X) indicate no restriction]		
			Chronic Use	Episodic Use	Comments or Exceptions
Any investigational drug		<30 days before Screening or 5 half-lives – whichever is longer	X	X	
Analgesics	Narcotic analgesics		X	X	Episodic use of opiates is allowed provided the subject has a valid prescription.
	NSAIDs		X		
	Cox-2 selective inhibitors				
	Acetaminophen				
Anorexics		2 weeks	X	X	
Antacids					
Antiacne agents					
Antianginal agents					
Antiarrhythmics of 1C class					Quinidine NOT allowed
Antibiotics					Rifampin NOT allowed
Antithrombic agents (including low dose aspirin) and anticoagulants			X	X	Low-molecular weight heparins are allowed for acute use
Anticonvulsants		2 weeks	X	X	
Antidepressants (including MAOIs and RIMAs)		2 weeks (5 weeks for fluoxetine)	X	X	
Antidiarrheal agents					

Footnotes are on last table page

Table 7.a Excluded Medications and Treatments (continued)

Drug Class	Disallowed Prior to Baseline I unless otherwise noted	Disallowed (X) During the Study [sections without (X) indicate no restriction]		
		Chronic Use	Episodic Use	Comments or Exceptions
Antifungal agents				
Antihistamines		X	X	Only loratadine, desloratadine, cetirizine, levocetirizine, mizolastine and fexofenadine are allowed
Antihypertensives				
Anti-impotence agents				
Antimigraine agents – Triptans, Dopamine antagonists	2 weeks	X	X	
Antinauseants, antiemetics (including dopamine antagonists)	2 weeks	X	X	Only phosphoric acid and bismuth preparations are allowed
Antineoplastics		X	X	
Antiobesity agents	2 weeks	X	X	
Antipsoriatic agents				
Antimalarial				
Antipsychotics	2 weeks (6 months for depot)	X	X	
Antiviral agents				
Anxiolytics (including benzodiazepines)	2 weeks	X	X	
Cough/cold agents		X		Allowed for episodic treatment for a maximum of 1 week
Diuretics				
Herbal remedies, which are psychoactive (eg, St. Johns Wort, kava kava, valerian, ginkgo biloba, melatonin)	2 weeks	X	X	
H2 Blockers Proton pump inhibitors				
Hormones		X	X	Thyroid hormone replacement, parathyroid hormone, and its recombinant form (Forteo), contraceptives (oral, patch, injectables and implants), estrogen and progesterone replacement therapy as well as benign prostatic hyperplasia treatment are allowed
Hypoglycemic agents			X	
Hypolipidemics				

Footnotes are on last table page.

Table 7.a Excluded Medications and Treatments (continued)

Drug Class		Disallowed Prior to Baseline I unless otherwise noted	Disallowed (X) During the Study [sections without (X) indicate no restriction]		
			Chronic Use	Episodic Use	Comments or Exceptions
Insulin				X	
Laxatives					
Mood stabilizers		2 weeks	X	X	
Psychotropic agents not otherwise specified (including stimulants, tryptophan, melatonin and dopamine agonists)		2 weeks	X	X	
Sedatives/hypnotics		2 weeks (see comments)	X		From 2 weeks to Baseline I to the end of the study, only zolpidem, eszopiclone/zopiclone, zaleplon, ramelteon allowed, with a maximum of 2 nights per week, and not the night before a study visit
Steroids:	Systemic	2 weeks	X	X	Injectable steroids are also not allowed.
	Topical				
	Inhalant				
Vaccines					

COX-2=cyclooxygenase-2, MAOI=monoamine oxidase inhibitor, NSAID =nonsteroidal anti-inflammatory drug, RIMA=reversible inhibitor of monoamine oxidase type A, H2 Blockers=H2 receptor antagonists (acid reducers)

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.18.

Applies to either Open-Label or Double-Blind Periods of Study.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver Function Test (LFT) Abnormalities

     Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study medication treatment:

     – ALT or AST >8 × ULN, or

     – ALT or AST >5 × ULN and persists for more than 2 weeks, or

- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
- ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Noncompliance with study drug. This includes subjects who did not take the study medication for 6 of more consecutive days or are less than 70% compliant between visits. NOTE: if noncompliance occurred during the Double-Blind phase and was preceded by a relapse to depression, then the main reason for withdrawal should be "relapse".
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or for relapse) should not be recorded in this category.
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.
9. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

Applies to Open-label Period ONLY:

1. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
2. Subject did not meet randomization criteria (response or remission criteria as specified in Section 7.3).

Applies to Double-Blind Period ONLY:

1. Relapse.
   a) MADRS ≥22.
   b) Lack of efficacy that is indicative of relapse per Investigator judgment.

c) Other unsatisfactory treatment response indicative of relapse as determined by Investigator (eg, subject hospitalization for depression, medication prescribed for MDD, electroconvulsive therapy, suicide attempt, etc.)

Note: A Relapse Checklist will be used by sites to evaluate potential indicators of relapse for each subject at each visit post baseline during the double blind-period.

7.6 Additional Guidance for Withdrawal Criteria

Throughout the study, signs of suicidal risk will be assessed by both the C-SSRS and MADRS assessment and the investigator's clinical judgment. If the subject has a significant risk of suicide according to the investigator or has a score of ≥5 on item 10 (suicide ideation) of the MADRS, the subject should be withdrawn from study. Significant risk of suicide would likely be indicative of relapse or pending relapse. This should be taken into consideration as reason for withdrawal in the Double-Blind Period.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Withdrawal Visit. Discontinued or withdrawn subjects will not be replaced.

Note: All procedures for the Withdrawal Visit should be performed regardless of the reason for withdrawal, with the exception of subjects who refuse any further contact.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

- Commercial vortioxetine (Brintellix) tablets in encapsulated strengths of 5, 10, and 20 mg
- Matching placebo capsules.

Vortioxetine 5, 10, and 20 mg tablets are manufactured by Takeda or H. Lundbeck A/S, Valby, Denmark. Overencapsulation (OE) of vortioxetine tablets and the manufacture of the placebo capsules using Swedish-Orange capsules with lactose monohydrate filler is by Almac Clinical Services, Souderton, PA USA

The study medication will be packaged in bottles with child resistant closures. Each bottle contains 14 daily doses plus 4 extra capsules for a total of 18 capsules per bottle. The daily dose is 1 capsule by oral administration.

OE vortioxetine 10 mg bottles will be labeled and dispensed as open labeled for the initial acute treatment phase. OE vortioxetine 5, 10, 20 mg and placebo bottles will be labeled and dispensed as double-blind for the relapse prevention treatment phase. Each label will contain pertinent study information.

8.1.1.1 Investigational drug

Vortioxetine is a novel compound developed by Takeda and H. Lundbeck A/S as an antidepressant and treatment for MDD. Vortioxetine belongs to a new chemical class of psychotropics, the bis-aryl-sulfayl amines, which possess unique properties compared with currently known psychotropics. This new class of compounds is structurally different from all currently known psychotropics.

Vortioxetine is commercially formulated as immediate release (IR) tablets intended for oral administration. The study medication is film-coated tablets containing hydrobromide salt of LuAA21004. The tablets contain Lu AA21004-HBr corresponding to 5, 10, and 20 mg of LuAA21004 base. Well known excipients are used to manufacture the tablet cores.

8.1.1.2 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

- Commercial vortioxetine tablets in encapsulated strengths of 5, 10, and 20 mg.
- Matching placebo capsules.

8.1.2 Storage

Study medication should be stored at 25ºC (77ºF) excursions permitted to 15 ºC to 30ºC (59 ºF -86ºF).

Investigational drug, OE vortioxetine 5, 10, and 20 mg and matching placebo must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug, OE vortioxetine 5, 10, and 20 mg and matching placebo must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The investigator or designee should contact the interactive web response system (IWRS) to register each subject at the initial screening visit. At each applicable study visit (Visits 2-18), the investigator or designee should contact the IWRS to receive the appropriate investigational medication assignment for dispensation. The IWRS will provide the medication identification (ID) number for each bottle dispensed at each study visit. The medication ID number assigned should be recorded in the source document and eCRF.

Each subject who qualifies following the initial screening visit will enter the 16-week open-label acute treatment phase and will be dispensed OE vortioxetine 10 mg.

Subjects will be instructed to take 1 capsule per day, orally, at the same time of day, preferably in the morning, or as directed. The first dose is to be taken the day after the study medication has been dispensed to the subject. Study medication can be taken with or without food. The subject should be advised to be consistent in the dosing time throughout the duration of the trial.

Subjects who qualify for randomization into the double-blind treatment period at week 16 (Visit 10) will be randomly assigned to 1 of 4 treatment groups: Vortioxetine 5, 10, 20 mg or placebo through the IWRS and will be dispensed the blinded study medication.

Subjects who complete the 16 week open-label acute treatment phase and the 32 week double-blind relapse prevention phase will receive a total of 24 bottles of study medication.

The investigator or designee will instruct the subject on the dosing procedures and investigational medication storage requirements. Subjects should return their unused investigational medication at each study visit to allow the opportunity for the investigator or designee to evaluate subjects' compliance with the dosing instructions

Table 8.a describes the daily dose and tablet count that will be provided to each group.

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
		Active	Placebo
Open-label	10 mg Vortioxetine QD	1 capsule containing one 10 mg vortioxetine tablet	0 placebo capsules
A	Placebo QD	0 active tablets/capsules	1 placebo capsule
B	5 mg Vortioxetine QD	1 capsule containing one 5 mg vortioxeting tablet	0 placebo capsules
C	10 mg Vortioxetine QD	1 capsule containing one 10 mg vortioxetine tablet	0 placebo capsules
D	20 mg Vortioxetine QD	1 capsule containing one 20 mg vortioxetine tablet	0 placebo capsules

QD = once daily

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, general symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measure employed.

As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdose.

8.2 Investigational Drug Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IWRS at Screening to obtain the subject study number. The investigator or the investigator's designee will utilize the IWRS to enroll the subject into the open-label acute treatment at the Baseline 1 visit should they qualify, where subjects will be dispensed OE vortioxetine 10 mg. The investigator or investigator's designee will access the IWRS to randomize the subject into the study should they meet the eligibility

requirements. Subjects will be assigned in a 1:1:1:1 ratio to one of the 4 treatment arms of Vortioxetine 5, 10, or 20 mg or placebo. Subject randomization across treatments will be balanced at the site level.

During each IWRS contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication ID number(s) of the investigational drug necessary to support the visit schedule to be dispensed will then be provided by the IWRS. If sponsor-supplied drug is lost or damaged, the site can request a replacement from the IWRS (refer to IWRS manual provided separately.) The medication ID number(s) will be entered onto the eCRF. At subsequent drug-dispensing visits, the investigator or designee will again contact the IWRS to request additional investigational drug for a subject. The medication ID number of the investigational drug to be dispensed will be provided by the IWRS. The medication ID number will be entered onto the eCRF.

Subjects should be instructed for the following:

- The sponsor-supplied drug is to remain in original container until time of dosing
- The subject should take only one tablet per day as instructed. If the dose is missed in the morning, it is acceptable to take the dose later in the same day. If the subject misses a dose, he/she should not take twice the dosing the next day.
- To store their sponsor-supplied drug according to the label and to keep out of the reach of children.
- Subjects are to return their sponsor-supplied drug at each visit.

8.3 Randomization Code Creation and Storage

Takeda randomization personnel or designee will generate the randomization schedule for the study; an IWRS will be used in a centralized fashion for subject randomization and study medication assignments.

All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IWRS. The principal investigator (PI) at each study site will receive instructions for obtaining the medication assignment through the IWRS. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of double-blind study medication unassigned and assigned treatment bottles. All assigned/unassigned treatment bottles will be reconciled and returned to the sponsor or a designee before study closure.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. If

possible, the sponsor/designee should be notified before the investigational drug blind is broken. If a medical emergency requiring unblinding occurs, the investigator (or designee) at the site will contact the sponsor or designee (see medical monitor contact information listed in Section 1.1) to assess the necessity to break the investigational drug blind.

For unblinding a subject, the investigational drug blind can be obtained by accessing the IWRS. The sponsor/designee must be notified immediately if the study medication blind is broken. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

If any site personnel is unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study. The reason for withdrawal should be recorded as "Protocol Deviation".

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (Vortioxetine 5, 10, 20 mg and placebo), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or Medication ID number) used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (Vortioxetine 5, 10, 20 mg and placebo) on a sponsor-approved drug accountability log/IWRS. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log/IWRS.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting a blood sample for pharmacogenomic research for this study. The provision of consent to collect and analyze the pharmacogenomic sample is independent of consent to the other aspects of the study.

9.1.1.2 Clinical Trial Subject Database (CTSdatabase) Authorization

A separate subject authorization will be obtained at the Screening Visit that will allow sites to enter specific subject information into CTSdatabase, a clinical trial registry.

9.1.2 CTSdatabase and Subject Database Authorization

Clinical trial registries, such as CTSdatabase, seek to reduce subjects from enrolling into multiple clinical trials by identifying duplicates before enrollment. At the time of providing the informed consent for the study, the Investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

During screen, site staff that have received training and login information access www.ctsdatabase.com and enter the subject study ID and authorized subject identifiers. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days or (3) the subject matches with a subject who has pre-screened at another site.

9.1.3 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.11).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 90 days prior to signing of informed consent.

9.1.4 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. Genitourinary examination will not be required.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.5 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature (oral or tympanic), pulse (beats per minute [bpm]), and sitting blood pressure (taken after 5 minutes in the sitting position).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained before or after the scheduled blood draw.

9.1.7 Diagnostic Assessment

Axis I disorders will be diagnosed according to DSM-IV-TR criteria. The assessment of MDE will be standardized by using the MINI. The MINI will also be used to evaluate the presence of comorbid psychiatric disorders in order to assess the appropriateness of the subject for inclusion.

9.1.7.1 MINI International Neuropsychiatric Interview

The MINI is a short structured diagnostic interview developed jointly by psychiatrists and clinicians in the United States and Europe for DSM-IV and International Classification of Diseases 10th Revision psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies. It is to be used as a first step in outcome tracking in nonresearch clinical settings. Validation and reliability studies have been done

comparing the MINI to the Structured Clinical Interview for DSM-IV, Patient Edition and the Composite International Diagnostic Interview. The results of these studies showed that the MINI has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7±11.6 minutes, median 15 minutes) than the above referenced instruments. The clinician responsible for the subject must administer the MINI [18-20].

9.1.7.2 Subject-completed Diagnostic Validation

Subjects will complete a computer-administered Diagnostic Validation (DvX) assessment at the Screening Visit prior to the rater-administered MINI, on a laptop or tablet provided to the site. The DxV will collect data about the subjects' history relative to lifelong history of MDD. The subject's diagnostic information based on the responses to the computerized interview will be reviewed by the rater vendor's clinician, and any uncertainty raised by the subject's responses on the diagnostic interview will be discussed with the Investigator/site clinician in order to establish confidence in the diagnosis. Subjects for whom diagnostic agreement between the Investigator/site clinician and the rater vendor clinician cannot be reached, may not be appropriate for study participation.

9.1.8 Primary Efficacy Measurements

The following assessments will be performed during the open-label and double-blind treatment periods, unless otherwise indicated:

- Prompted MADRS/Structured Interview Guide for the MADRS (SIGMA).
- CGI-S.
- CGI-I (CGI-I will be assessed during the open-label period; and at Baseline II and Completion/Withdrawal during the double-blind period).

9.1.9 Psychiatric/Neurological Rating Scales

MADRS

The MADRS is a depression rating scale consisting of 10 items, each rated 0 to 6. The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the subject, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Nine of the items are based upon subject report, and 1 is based on the observation of the subjects. The Prompted Assessment does prompt the rater to ask the subject questions in assessing this item (apparent sadness). The clinician, who conducts the rating, must decide whether the rating for each item lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). Decrease in the total score or on individual items indicates improvement [13].

The MADRS will be assessed by the rater utilizing the laptop/tablet provided to the site in a prompted assessment fashion. The Prompted Assessment incorporates questions and decision trees in a semi-structured format. Based on the responses entered into the laptop/tablet by the rater, the computer will determine once enough information has been collected to accurately score each

item. Raters are encouraged to ask additional questions as needed in order to score each item. The scores are recorded into the laptop/tablet and serve as the source for the study.

SIGMA

Sites may choose, in addition to the Prompted Assessment, to utilize the SIGMA to assist in assessing the MADRS; however, this is not required. The SIGMA was created to standardize the administration of the MADRS and ensure comprehensive coverage of MADRS items through the use of structured questions. The SIGMA questions were developed to obtain the information needed to assess each of the items' anchor points. In the SIGMA, the original MADRS appears on the right-hand side of the page and the structured interview guide questions appear on the left [14]. If a site chooses to use the SIGMA it must be used for all visits for an individual subject.

Clinical Global Impression Scales

The CGI scales [15] consist of 2 subscales: the CGI-S and the CGI-I.

The CGI-S assesses the clinician's impression of the subject's current mental illness state. The clinician should use his/her total clinical experience with this patient population and rate the current severity of the subject's mental illness on a 7-point scale.

The CGI-I assesses the subject's improvement (or worsening). The clinician is required to assess the subject's condition relative to Baseline I (baseline at start of treatment) on a 7-point scale. In all cases, the assessment should be made independent of whether the rater believes the improvement/worsening is drug-related or not.

The rater will enter their CGI-S and CGI-I scores directly on the laptop/tablet provided to the site. When these scores are recorded in the laptop/tablet, they will serve as the source for the study.

9.1.9.1 Order of Psychiatric/Neurological Rating Scales/Assessments

Sites should make every attempt to complete the assessments in the following order:

Diagnostic Validation (DvX) (Screening only).

MINI (Screening only).

MADRS via Prompted Assessment.

C-SSRS.

CGI-S.

9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.11 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG or physical examination abnormalities noted at screening or Baseline I examination. The condition (ie, diagnosis) should be described.

9.1.12 Procedures for Clinical Laboratory Samples

Laboratory samples will be taken at the time points stipulated in the Schedule of Study Procedures; samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 29 mL, and the approximate total volume of blood for the study is 186 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual. Appendix E describes procedures for specimen handling.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	ALT	Specific gravity
WBC	Albumin	pH (dipstick)
Hemoglobin	Alkaline phosphatase	Glucose (dipstick)
Hematocrit	AST	Protein (dipstick)
Platelets	Total protein	Occult blood (dipstick)
Neutrophils	Creatinine	Microscopic battery:
Eosinophils	Blood urea nitrogen	(WBC, RBC, epithelial
Basophils	Creatine kinase	cells, casts) (d)
Lymphocytes	GGT	
Monocytes	Potassium	
HbA1c(a)	Sodium	
	Total bilirubin	
	Direct bilirubin (b)	
	Calcium	
	Glucose (fasting or nonfasting) (c)	
	Lipids (fasting or nonfasting) (c)	
	Cholesterol total	
	Triglycerides	
	High-density lipoprotein	
	Low-density lipoprotein	

Other:

Serum	Urine
HBsAg (a)	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, sedatives, narcotics, opiates, and alcohol (f).
HCV (a)	
TSH, free thyroxine (e)	
Female subjects of childbearing potential	Female subjects of childbearing potential
hCG for pregnancy	hCG for pregnancy

Footnotes are on last table page.

GGT=γ-glutamyl transferase, hCG=human chorionic gonadotropin, RBC-red blood cells, WBC=white blood cells.
(a) To be done at Screening only.
(b) Assess only if total bilirubin ≥2 mg/dL.
(c) Fasting labs will be performed at Baseline I, Baseline II/Randomization or Withdrawal from open-label, and Completion/Withdrawal of double-blind.
(d) Microscopic examination of sediment will be performed only if the dipstick results are positive
(e) TSH assessed at **screening** in order to exclude subjects with clinically significant thyroid dysfunction (hyperthyroidism or hypothyroidism), which may mimic symptoms of depression and anxiety. If TSH value is outside the normal range, a free T4 will be obtained.
(f) To be done at Screening, Baseline I, and Baseline II/Randomization and at any time per Investigator discretion.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who will be responsible for filing and reviewing these results together with the data in the eCRF. The investigator is responsible for recording the interpretation of clinical significance of any abnormal laboratory results in the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.1.5.2 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.1.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

9.1.13 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 2 years since last regular menses).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.
- Progesterone T PLUS condom or spermicide.

Hormonal contraceptives:

- Implants.
- Hormone shot/injection.
- Combined pill.
- Minipill.
- Patch.
- Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at the Baseline 1 Visit prior to receiving any dose of study medication.

9.1.14 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (vortioxetine or placebo) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Baseline l Visit or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time

she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.15 ECG Procedure

A standard 12-lead ECG will be recorded. The following parameters will be recorded electronically by a central reader from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval and corrected QT interval (QTc). The central reader will interpret the ECG using 1 of the following categories: within normal limits or abnormal. If interpreted as abnormal, the investigator will assess the findings as either abnormal clinically significant, or abnormal not clinically significant. The interpretation of the ECG will be recorded in the source documents and in the eCRF. ECG traces recorded on thermal paper will be photocopied to avoid degradation of trace over time. Requirements for the ECG equipment and procedure for collecting and transferring information to the central reader will be provided in the site manual.

9.1.16 Pharmacogenomic Sample Collection

When sampling of whole blood for pharmacogenomic analysis occurs, every subject must sign informed consent/be consented in order to participate in the pharmacogenomic sample analysis.

Two 3-mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day 0 from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K2EDTA) spray-coated tubes, and stored under frozen conditions.

Two whole blood samples (2.5 mL per sample) will be collected at each time point at predose on Day 0, Week 8 (Visit 6), Week 16 (Visit 10) and Week 48 (Completion/Early Termination) for ribonucleic acid (RNA) pharmacogenomic analysis from each subject in the study, into a PaxGene ™ tube. For subjects who withdraw during the open-label treatment period, a blood sample will be collected at study termination, regardless of the treatment duration.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "Pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to vortioxetine.
- Finding out more information about how vortioxetine works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to vortioxetine.
- Identifying variations in genes related to the biological target of vortioxetine.

This information may be used, for example, to develop a better understanding of the safety and efficacy of vortioxetine and other study medications, and for improving the efficiency, design and study methods of future research studies.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with a 7-digit subject ID (the 4-digit site number plus the 3-digit subject number).

The pharmacogenomic samples will be shipped to PPD for initial study storage and then to Covance Central Lab for long term storage.

A portion of the DNA sample may be analyzed for the presence of, eg, allelic variants in drug metabolizing enzymes, drug transporters, or putative drug targets.

The samples will be stored for no longer than 15 years after completion of the study or vortioxetine is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda.

"Stored samples" are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drugs.

Detailed instructions for the handling and shipping of samples are provided in Appendix E.

9.1.17 Pharmacokinetic Sample Collection and Analysis

9.1.17.1 Collection of Plasma for Pharmacokinetic Sampling

All subjects will participate in plasma sampling collection. The subject(s) will have 2 blood samples to be collected at Week 8 (Visit 6) and Week 16 (Visit 10). The sample should be collected prior to randomization at Week 16 (Visit 10). For subjects who withdraw during the open-label treatment period, blood samples will be collected at study termination, regardless of the treatment duration. Following randomization on Week 16 (Visit 10), 2 additional blood samples from each subject will be collected at Week 32 (Visit 15) and Week 48 (Completion/Early Termination). The blood samples for pharmacokinetic analysis will be collected at the same time points as the blood sample for clinical laboratory tests. At Visits 10, 15 and Completion sites are encouraged to schedule the blood draw to occur after the subject has taken his/her study medication that day. The plasma samples will be analyzed for plasma concentration of vortioxetine (LuAA21004) by validated method. The approximate blood collection is 6 mL per scheduled time point.

For all participating subjects, the exact date and time of the plasma sample collection and the two last doses taken prior to the plasma sampling will be documented in the source documents and captured in the eCRFs. Please refer to Appendix E for instructions for the collection, handling and shipping of plasma samples for pharmacokinetic analysis. Placebo samples will not be analyzed by

the bioanalytical laboratory, and the bioanalytical laboratory will be unblinded to select those patients receiving placebo.

9.1.17.2 Bioanalytical Methods

Plasma concentrations of vortioxetine will be measured by high-performance liquid chromatography with tandem mass spectrometry.

9.1.18 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this screening or Baseline I visit, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason)
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.19 Documentation of Re-Screening

Re-screening of subjects who do not meet eligibility requirements is not allowed. If the PI believes in the appropriateness of the subject for the study and considers a re-screen, permission for this must be obtained from Medical Monitor. Re-screening at the investigator's discretion without prior approval from the medical monitor is not permitted.

9.1.20 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.21 Rater Qualification and Certification Process

In order to ensure collection of quality data from scales administered by raters, raters assigned to this study will be required to fulfill qualification and certification requirements. Furthermore, the

study will include additional steps related to monitoring the quality of rater activity which is described in Section 9.1.22.

The rater academic degree and experience required will be defined and collected for each rater by completion of a questionnaire. Raters must be qualified by this process prior to completing any training or attending the Investigator Meeting. Raters meeting qualification criteria must also complete the certification process on the MADRS.

All raters will be required to successfully fulfill the full scope of rater training requirements for any scale they will be administering prior to rating any subjects in this study. Raters who successfully meet all requirements will be approved for participation in the study by Takeda and/or its designee before enrollment may commence at sites. Raters who do not meet all the qualification and training requirements may be prohibited from participating as raters on this study. Takeda and/or its designee may revoke a rater's certification during the study.

The training materials and requirements may be adjusted or modified as needed throughout the course of the study.

9.1.21.1 Prior to Study Start

Rater Qualifications

Each site will be required to identify and provide skilled raters who meet appropriate prespecified qualifications. Takeda and/or its designee will make the final decision regarding whether the site assigned raters are acceptable to participate in the study.

Note: The investigator responsible for the subject must be the only one to rate the subject using the CGI. The investigator is defined as a clinician with suitable training and experience as deemed by the sponsor.

Submission of Experience Details:

Raters will be required to complete and submit experience details and curriculum vitae (if applicable) to the rater vendor in a timely manner. Once the rater's experience level is reviewed and deemed adequate then study assigned raters will be approved to participate in the rater certification process.

9.1.21.2 Report Training Certification

Formal rater training and certification will be conducted at the Investigator Meeting, For those raters who need to be trained outside of the Investigator Meeting, the training will be conducted via web portal or digital versatile disc (DVD). Rater training curriculum will be comprised of some or all of the following elements:

- Training presentation for the protocol instruments capturing background and study conventions related to administration and interview skills for protocol related scales and placebo response training.
- Viewing and scoring of videotaped MADRS interviews.

- Interview skills training and assessment.

Training and/or certification is required in order for a rater to rate the scales in the study. Raters that meet a predefined MADRS scoring and interview skills proficiency threshold will be issued MADRS certification. Raters that do not meet the threshold will be subject to additional training and an individual assessment by a clinician from the rater training vendor. MADRS certification and secondary scale qualification documents for each rater will be provided to sites and maintained by the rater training vendor throughout the study.

Enrollment at the site may not commence until the respective site rater has been informed that they have met the necessary certification requirements. Raters who receive an unacceptable rating will be required to complete additional training in conjunction with the Takeda designated rater training vendor.

9.1.21.3 Site Changes to Rater Personnel during the Study

If a site rater changes during the course of the study, the newly appointed rater must be approved by Takeda for participation and must complete all training and certification requirements satisfactorily before the rater can begin participation on any study related activities.

9.1.22 Rater Monitoring

Computerized scores will be generated during the Prompted Assessments for the MADRS and CGI. The computerized scores are utilized as post-interview quality control by the rater vendor, but the rater assigned scores entered into the computer are the outcome scores documented. Rater assigned scores are not changed based on the outcome of the Prompted Assessment computerized scores, but are used for ongoing quality control and to increase the precision and validity of clinician ratings.

Additional scale data will be monitored for consistency and quality control throughout the trial. Further instructional activities or advisement will occur and may be requested for certain sites if necessary.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers/unused medications to each dispensing site visit regardless of whether or not the study medication container is empty.

If a subject is persistently noncompliant with the study medication (eg, 6 or more consecutive doses missed in any given week; less than 70% compliant between visits), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A.

Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Visit 1 (Days -21 to -5)

Subjects will be screened within 21 to 5 days prior to Baseline I (Day 0). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting screening failures.

Sites will complete a pre-enrollment form for subjects who meet the screening requirements. The form will be submitted to the contract research organization (CRO) for medical monitor review and confirmation of certain inclusion/exclusion criteria. The sponsor reserves the right to utilize external quality oversight methods to ensure the validity of diagnosis, severity of illness, and other factors in determining appropriateness of subject selection.

Procedures to be completed at Screening Visit 1 include:

- Informed consent.
- CTSdatabase Authorization.
- Demographics, medical history, and medication history.
- Pretreatment event assessment.
- Concurrent medical conditions.
- Relevant psychiatric and social history.
- Diagnostic validation.
- MINI.
- Vital signs.
- Weight, height.
- Physical examination.
- Concomitant medications.
- Screening clinical laboratory tests, urine drug screen, serum hCG pregnancy test.
- ECG procedure.
- Pregnancy avoidance counseling.
- C-SSRS.
- Prompted MADRS.
- Assess inclusion/exclusion criteria/eligibility verification.
- Access IWRS to obtain subject number.

9.3.2 Study Entrance into Open-Label Treatment; Baseline I, Visit 2 (Day 0)

Study entrance will take place on Day 0. The following procedures will be performed and documented during Baseline I:

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for enrollment into Open-Label Treatment, the subject should be enrolled using the IWRS as described in Section 8.2. Subjects will be instructed on when to take the first dose of investigational drug as described in Section 8.1.3. The procedure for documenting Screening failures is provided in Section 9.1.18.

- Concurrent medical conditions.
- Assess inclusion/exclusion criteria.
- Pretreatment event assessment.
- Vital signs.
- Weight.
- Physical examination.
- Concomitant medications.
- Clinical laboratory tests, urine drug screen, urine pregnancy test.
- ECG procedure.
- Pregnancy avoidance counseling.
- C-SSRS.
- MADRS.
- CGI-S.
- Pharmacogenomic sample (DNA and RNA).
- Access IWRS for medication ID.
- Dispense study medication.

9.3.3 Open-Label Treatment Visits 3-9, Weeks 2, 4, 6, 8, 10, 12, and 14 (± 3 days)

- Vital signs.
- Weight (*week 8 only*).
- Concomitant medication.
- Clinical laboratory test (*week 8 only*).
- Urine pregnancy test.

- Pregnancy avoidance counseling.
- C-SSRS.
- Adverse events assessment.
- MADRS.
- CGI-S.
- CGI-I.
- Stabilization criteria (*Weeks 8, 10, 12, and 14*).
- PK sampling for study medication (*week 8 only*).
- Pharmacogenomic sampling RNA (*Week 8 only*).
- Access IWRS for medication ID.
- Dispense study medication.
- Study medication return/accountability/compliance.

9.3.4 Withdrawal Visit from Open-label Treatment (± 3 days)

This visit will be performed for any subject that does not meet response or remission criteria during open-label period or has met other withdrawal criteria outlined in Section7.5. The following procedures will be performed and documented.

- Vital signs.
- Weight.
- Physical examination.
- Concomitant medication.
- Clinical laboratory test, serum hCG pregnancy test.
- PK sampling for study medication.
- Pharmacogenomic sampling RNA.
- ECG.
- Pregnancy avoidance counseling.
- C-SSRS.
- Adverse events assessment.
- MADRS.
- CGI-S.

- CGI-I.
- Access IWRS for subject status.
- Study medication return/accountability/compliance.

9.3.5 Baseline II Randomization, Visit 10, Week 16 (± 3 days)

At baseline II subjects who have met the randomization criteria (response and remission) and have not met any withdrawal criteria will be randomized in the double-blind treatment.

- Stabilization criteria.
- Randomization criteria.
- Vital signs.
- Weight.
- Physical examination.
- Concomitant medication.
- Clinical laboratory test.
- Urine drug test.
- ECG.
- Serum hCG pregnancy test.
- Pregnancy avoidance counseling.
- C-SSRS.
- Adverse events assessment.
- MADRS.
- CGI-S.
- CGI-I.
- PK sampling for study medication.
- Pharmacogenomic sample (RNA only).
- Access IWRS for medication ID.
- Dispense study medication.
- Study medication return/accountability/compliance.

9.3.6 Double-Blind Treatment, Visits 11 and 12, Week 18 (± 3 days) and Week 20 (± 5 days)

- Vital signs.
- Weight (*week 18 only).*
- Physical examination (*week 18 only).*
- Concomitant medication.
- Clinical laboratory test (*week 18 only).*
- Urine pregnancy test.
- Pregnancy avoidance counseling.
- C-SSRS.
- Adverse events assessment.
- Relapse Checklist.
- MADRS.
- CGI-S.
- Access IWRS for medication ID.
- Dispense study medication.
- Study medication return/accountability/compliance.

9.3.7 Double-Blind Treatment Subject Well Being Calls Weeks 22, 26, 30, 34, 38, 42, and 46

Subjects will be called to check on status and reminded about study visits, study medication compliance, assess adverse events, and assess for any relapse.

9.3.8 Double-Blind Treatment Visits 13-18, Weeks 24, 28, 32, 36, 40, and 44 (± 5 days)

- Vital signs.
- Weight (*weeks 24, 32, and 40 only).*
- Physical examination (*week 32 only).*
- Concomitant medication.
- Clinical laboratory test (*week 32 only).*
- ECG *(week 32 only).*
- Urine pregnancy test.

- Pregnancy avoidance counseling.
- C-SSRS.
- Adverse events assessment.
- Relapse Checklist.
- MADRS.
- CGI-S.
- PK sampling for study medication (*week 32 only).*
- Access IWRS for medication ID.
- Dispense study medication.
- Study medication return/accountability/compliance.

9.3.9 Completion/Withdrawal from Double-Blind, Visit19, Week 48 (± 5 days)

The Final Visit will be performed on week 48 for a completed subject or at the withdrawal visit for a subject who withdrawals from the study early. This visit will be performed for any subject who relapses during double-blind period or has met other withdrawal criteria outlined in Section7.5. The following procedures will be performed and documented:

- Vital signs.
- Weight.
- Physical examination.
- Concomitant medication.
- Clinical laboratory test.
- ECG.
- Serum hCG pregnancy test.
- Pregnancy avoidance counseling.
- C-SSRS.
- Adverse events assessment.
- Relapse Checklist.
- MADRS.
- CGI-S.
- CGI-I.
- PK sampling for study medication.

- Pharmacogenomic sampling (RNA only).
- Access IWRS for subject status.
- Study medication return/accountability/compliance.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.10 Safety Follow-up Phone Call

A safety follow-up phone call will be made 30 days (± 5 days) after withdrawal from either open label or double-blind treatment or after completion of study. The following procedures will be performed:

- Concomitant medications.
- AE assessment.

9.3.11 Post-Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

9.4 Biological Sample Retention and Destruction

The pharmacogenomic samples will be preserved and retained at Covance Central Lab for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The samples will be initially stored at PPD Central Labs prior to being transferred to Covance Central Lab. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy. Note that lack of efficacy during double-blind treatment should be recorded as a relapse.

Suicidality events:

- A completed suicide is always an SAE based on its fatal outcome. Additionally, for the purpose of this development program, active suicidal behaviors such as "suicidal intention with a definite plan" and "suicide attempt" will also be collected as SAEs. Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or action will be collected as nonserious AEs in accordance with the standard AE reporting requirements (eg, if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE). A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the eCRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as an SAE. Acts of self-mutilation or self-injury without suicidal intention, for example, self-imposed cigarette burns, will be collected as nonserious AEs.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
1. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

2. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
3. Results in persistent or significant DISABILITY/INCAPACITY.
4. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
5. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

10.1.5.1 Skin and Allergic Type Reactions

Any subject who develops rash should undergo assessment to characterize the nature and location of the rash. Subjects should be adequately examined for any clinical features that might suggest a developing drug reaction with eosinophilia and systemic symptoms (DRESS), a developing toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS). For example, all subjects who develop rash should undergo a physical examination and be monitored for the appearance of any of the following features (and findings should be recorded):

a) Involvement of mucous membranes or conjunctiva.

b) The development of skin pain.

c) Urticaria, blistering, other skin lesions.

d) Any evidence of angioedema.

If there are subjects with symptoms of systemic reaction (eg, generalized rash), or signs of a severe rash (such as those outlined above) or if clinically appropriate then the following laboratory parameters should also be conducted and monitored accordingly: complete blood count with differentials, liver and renal functions tests, and urinalysis.

Any subjects showing symptoms or signs outlined above or if clinically indicated should also be assessed by a dermatologist and undergo an adequate diagnostic work-up (to assess for developing DRESS, TEN, or SJS).

Finally, consider taking photographs of rashes and, when appropriate, obtain skin biopsies.

For all cases of rash where an alternative causality is not known a skin or allergy type reaction eCRF form should be completed within 1 business day of the investigator's awareness of the event. If the alternative causality has been identified, then no skin or allergy type reaction eCRF should be completed.

10.1.5.2 Liver Injury

Management of liver toxicity AEs is described in Section 7.5 of the protocol. If ALT or AST >3×ULN, laboratory tests should be repeated within a maximum of 7 days, and preferably within 48 to 72 hours. If the ALT or AST remains elevated >3×ULN on these 2 consecutive occasions, and this observation cannot be explained by concomitant disease or another alternative causality, the abnormality should be recorded on an AE page. The investigator must contact the Medical Monitor for consideration of immediate discontinuation of study medication, discussion of the relevant subject details and possible alternative causalities.

For events that meet the criteria described in Section 7.5 of the protocol a liver injury eCRF form should be completed within 1 business day of the investigator's awareness of the event.

10.1.5.3 Overdose

Management of an overdose is described in Section 8.1.4 of this protocol. All cases of overdose (with or without associated AEs) will be documented as AEs. For events that meet the criteria of an

overdose, an overdose eCRF form should be completed within 1 business day of the investigator's awareness of the event.

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.

- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Baseline l Visit) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Baseline l Visit). Routine collection of AEs will continue for 30 days post the last dose of study medication.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

10.2.1.3 Special Interest AE Reporting

If the subject experiences a skin rash or allergic type event as described above, liver injury, or overdose during the treatment period or the safety follow-up period based on the criteria outlined in Section 10.1.5 the event should be reported on a specific eCRF form within 1 business day of the investigator's awareness. Any relevant supporting documentation (ie, photographs, additional diagnostic testing, consultation reports) must be submitted to the sponsor. The special interest AEs have to be recorded as AEs in the eCRF.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s)
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the eCRF report should be updated with the additional information within 24 hours of receipt. Copies of any relevant data from the hospital record (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs as applicable, in accordance with national regulations in the country where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her local IRB, if one is used.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Subject eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign.

Subject eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to

enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment/database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment/database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The full analysis set (FAS) will include all subjects who were randomized to the double-blind treatment period and received at least 1 dose of double-blind study drug after randomization. In FAS efficacy summaries, subjects will be analyzed by the treatment to which they were randomized.

A per protocol set (PPS) will include all FAS subjects who had no major protocol violations. Subjects to be excluded from the PPS, whether due to protocol violations or noncompliance to the dosing schedule, will be identified in the minutes of the subject evaluability assessment performed prior to unblinding.

The safety set will include all subjects who were enrolled into the study and received at least 1 dose of study medication. In safety summaries, subjects will be analyzed according to the treatment they received. In the event that a subject receives more than 1 treatment, the actual treatment will be defined as the 1 that is used most frequently. If the 2 most common treatments are used with equal frequency, then the randomized treatment will be used as the actual treatment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline characteristics will be listed and summarized for demographics (gender, age, race, and body mass index), physical examination including assessment of menopausal status and medical history including psychiatric history.

Baseline values for efficacy and safety parameters in both open-label and double-blind treatment periods will be in the standard tables summarizing data per visit; however, baseline efficacy data will also be presented separately based on all subjects randomized.

For continuous variables, comparability of treatment groups will be assessed using an analysis of variance with treatment and center as factors. For discrete variables, comparability will be assessed using the Cochran-Mantel-Haenszel general association test, stratified by center. The p-values will be displayed as descriptive statistics of comparability.

13.1.3 Efficacy Analysis

Primary Efficacy Analysis

The primary efficacy variable will be the time from randomization to relapse during the first 28 weeks of the 32-week double-blind treatment with relapse defined as depression (MADRS ≥22), or lack of efficacy as determined by the investigator (date of relapse – date of randomization +1). Primary analysis will be based on a Cox model with an exact method to handle ties (based on the FAS), with treatment as the factor and baseline MADRS total score as the covariate of the Cox model.

Secondary Efficacy Analyses

Change from double-blind Baseline II in MADRS total score will be analyzed using a mixed model for repeated measurements (MMRM) analysis with treatment, center, week, treatment-by-week interaction, baseline MADRS total score-by-week interaction as fixed effects, and a completely unstructured covariance matrix**.** Change in MADRS total score will also be analyzed using analysis of covariance (ANCOVA), with treatment and center as fixed factors, Baseline II MADRS total score as covariate, and using the last-observation-carried forward (LOCF) technique and observed case (OC) methods. Comparisons between the different doses of vortioxetine and placebo will be performed over all the assessment points. Ninety-five percent confidence intervals will be presented together with the estimated p-value and the ANCOVA tests will be 2-sided.

CGI-I scores and change from Baseline II in the CGI-S will be analyzed by study visit using both MMRM and ANCOVA similar to the ones described above for the change of MADRS total score.

Time from randomization to relapse of MDD occurring during the entire 32-week double-blind treatment period will be analyzed using a Cox model similar to the one described above for the primary variable.

Controlling Type I Error

To control the type I error of the study, comparison between each dose of vortioxetine and placebo will be tested in the sequential order of 20 mg vs placebo, 10 mg vs placebo, and 5 mg vs placebo at significance level 0.05; as soon as a dose is non-significant from placebo at 0.05, the testing procedure stops for all subsequent dose(s).

Additional Analyses

The time from randomization to withdrawal for any reason during 28 weeks of double-blind treatment, will be analyzed using a Cox model similar to the one described above for the primary variable.

C-SSRS will be summarized at all time points for each treatment group using descriptive techniques.

13.1.4 Pharmacokinetic Analysis

The population pharmacokinetics of vortioxetine will be assessed by means of nonlinear mixed effect modeling (NONMEM). Individual exposure parameters (eg, AUC_{τ}, C_{av}, C_{max}) will be estimated and their correlation with relevant pharmacodynamic parameters will be explored (efficacy and tolerability/safety) if necessary. A separate population pharmacokinetics analysis plan and report will be generated for the analysis.

Plasma concentrations of vortioxetine will be summarized by treatment and visits.

13.1.5 Safety Analysis

The safety data will be summarized for the open-label period and double-blind period separately.

Adverse Events

Adverse events will be reported throughout the study. The definition of treatment-emergent adverse events will be provided in the SAP. Adverse events will be coded using the MedDRA and will be summarized by system organ class and preferred term. Adverse events that were reported more than once by a subject during the same period will be counted only once for that subject and at period of the maximum severity.

Clinical Evaluations

Absolute values and changes from Baselines I and II in clinical safety laboratory tests, vital signs, ECG parameters, and weight/body mass index will be summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned. No early termination of the study is planned based on the number of relapses observed, all randomized subjects will be followed for 32 weeks of double-blind study.

13.3 Determination of Sample Size

Assuming a cumulative relapse rate at 28 weeks of 15% for the vortioxetine group versus 30% for the placebo group, a total of 600 subjects (150 per treatment group) will provide 85% power to find a statistically significant difference between each dose of vortioxetine and placebo at a 5% significance level.

It is anticipated that approximately 55% of the patients enrolled into the open-label period will qualify for the double-blind study phase. Therefore, a total of about 1100 patients will need to be enrolled into the open-label period of the study. However, if the number of subjects who relapsed during the double-blind treatment period is much less than expected, sample size adjustment will be considered. In addition, as the required number of subjects enrolled into the open-label period is dependent upon the number randomized into the double-blind, the number enrolled may be more or less than the estimated 1100.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening	Baseline I	Open-Label Treatment							Baseline II/ Random-ization(a)	Withdrawal (b)	Follow-up ☎ call
Study Day/End of Week:		**Day 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		
Visit Windows (Days relative to Baseline I)	**Days -21 to -5**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Screening/Baseline Procedures and Assessments												
Informed consent	X											
CTSdatabase	X(c)											
Demographics, medical history, height	X											
Concurrent medical conditions	X	X (d)										
Relevant psychiatric and social history	X											
Diagnostic Validation	X											
MINI	X											
Diagnosis (DSM-IV-TR)	X											
Medication history	X											
Inclusion/exclusion criteria	X	X (d)										
Eligibility verification	X											
Stabilization criteria (e)						X	X	X	X	X		
Randomization criteria										X		
Safety Assessments												
PTE assessment (f)	X	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Body weight	X	X				X				X	X	
Physical examination	X	X								X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X (g)
Clinical laboratory tests (h)	X	X				X				X	X	
Urine drug screening	X	X								X		
ECG	X	X								X	X	
Pregnancy test (hCG) (i)	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy avoidance counseling	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	
AE assessment			X	X	X	X	X	X	X	X	X	X (j)

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening	Baseline I	Open-Label Treatment							Baseline II/ Random-ization(a)	Withdrawal (b)	Follow-up ☎ call
Study Day/End of Week:		**Day 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**		
Visit Windows (Days relative to Baseline I)	**Days -21 to -5**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Efficacy Assessments												
MADRS (SIGMA if site chooses to use)	X	X	X	X	X	X	X	X	X	X	X	
CGI-S		X	X	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	X	X	X	
Other Blood Sampling												
PK sampling for study medication						X				X	X	
Pharmacogenomic sampling (h)		X				X				X	X	
Clinical Supplies												
Call IWRS for Subject ID/Medication ID/subject status	X	X	X	X	X	X	X	X	X	X	X	
Dispense study medication		X (k)	X	X	X	X	X	X	X	X		
Study medication return/ accountability/compliance			X	X	X	X	X	X	X	X	X	

(a) Subjects who meet all randomization criteria please follow schedule of procedures for week 16 on schedule of study procedures for double-blind treatment period.
(b) All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible.
(c) Obtain subject authorization, enter subject into the CTS database.
(d) Update at Baseline I.
(e) Subjects must meet response criteria from Week 8 through Week 16 and remission criteria at Weeks 14 and 16.
(f) Pretreatment event assessment occurs from the date of Screening up to the first dose of study medication.
(g)Assess post-treatment adverse events, ongoing adverse events and/or serious adverse events, and record all ongoing medications for subjects who withdraw early.
(h) Fasting labs must be performed at Baseline I and Baseline II (randomization).
(i) Serum hCG for female subject of childbearing potential at Screening, Baseline II (randomization) and Withdrawal. Urine stick pregnancy tests to be done at all other visits.
(j) Two whole blood samples (3 mL per sample) will be collected predose on Day 0 for DNA isolation. Two whole blood samples (2.5 mL per sample) will be collected for RNA isolation at each time point at predose on Day 0 and weeks 8, and 16 and any early withdrawal visit during open-label. The sample for pharmacogenomics may be drawn at the earliest visit after Baseline I, if missed at visit 2 (Baseline I). Pharmacogenomics sample collection is optional for subjects. A separate Informed Consent Form will be obtained.
(k) The subjects will be instructed to take the first dose of study medication on the morning after enrollment (Baseline I).

Appendix A Schedule of Study Procedures (continued)

	Baseline II/ Random-ization	Double-Blind Treatment (a)								Completion/ Withdrawal (b)	Follow-up ☎ call
End of Week:	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Windows (Days relative to Baseline II)	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Visit Number:	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
Baseline II Procedures and Assessments											
Randomization criteria	X (c)										
Safety Assessments											
Vital signs	X	X	X	X	X	X	X	X	X	X	
Body weight	X	X		X		X		X		X	
Physical examination	X	X				X				X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X(d)
Clinical laboratory tests (e)	X	X				X				X	
Urine drug screening	X										
ECG	X					X				X	
Pregnancy test (hCG) (f)	X	X	X	X	X	X	X	X	X	X	
Pregnancy avoidance counseling	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	
AE assessment	X	X	X	X	X	X	X	X	X	X	X(d)
Relapse Checklist		X	X	X	X	X	X	X	X	X	
Efficacy Asssessments											
MADRS (SIGMA if site chooses to use)	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	X	
CGI-I	X									X	
Other Blood Sampling											
PK sampling for study medication (g)	X					X				X	
Pharmacogenonic sampling (h)	X									X	
Clinical Supplies											
Call IWRS for Subject ID/Medication ID/subject status	X	X	X	X	X	X	X	X	X	X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Baseline II/ Random-ization	Double-Blind Treatment (a)								Completion/ Withdrawal (b)	Follow-up ☎ call
End of Week:	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Windows (Days relative to Baseline II)	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Visit Number:	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
Dispense study medication	X (i)	X	X	X	X	X	X	X	X		
Study medication return/ accountability/compliance	X	X	X	X	X	X	X	X	X	X	

(a) Subject well-being phone calls should be made every 2 weeks post Week 20 through week 46.
(b)All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible.
(c) Confirm stabilization criteria of response and remission are met and there are no major protocol violations.
(d)Assess post-treatment adverse events, ongoing adverse events and/or serious adverse events, and record all ongoing medications for subjects who withdraw early.
(e) Fasting labs to be performed at Baseline II/ Randomization and Completion/Withdrawal.
(f) Serum hCG for female subject of childbearing potential at Baseline II/Randomization and Completion/Withdrawal. Urine stick pregnancy tests to be done at all other visits.
(g) PK sampling must be taken prior to first dose of double-blind study medication.
(h) Only samples for RNA to be collected at Week 16 and Week 48 for those subjects who consented to pharmacogenomic sampling.
(i) The subjects will be instructed to take the first dose of study medication on the morning after randomization.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Collection, Shipment, and Storage of Pharmacogenomic Samples

Sample Collection

Two 3-mL whole blood sample for DNA isolation will be collected from each subject at the earliest study visit after randomization into a plastic tube spray coated with potassium ethylenediamine-tetraacetic acid (K2EDTA).

Two whole blood samples (2.5 mL per sample) will be collected at each time point at predose on Day 0 and week 8, week 16 and week 48/Early Termination visit for RNA pharmacogenomic analysis from each subject in the study, into a PaxGene ^{TM} tube. For subjects who withdraw during the open-label treatment period, a blood sample will be collected at study termination, regardless of the treatment duration.

Sample Shipment

Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday. The laboratory must confirm arrival of the shipped samples.

For instructions on shipping and packing follow the laboratory manual and shipping instructions provided by the central laboratory.

Before shipping, ensure the sample tubes are tightly sealed.

PPD will do the initial study period storage of the DNA and RNA samples. The samples will be shipped to Covance Laboratories for long term storage. Covance will store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on vortioxetine continues for 15 years or as required by applicable law.

Samples should be shipped as per conditions detailed in the lab manual.

The storage provider has validated procedures in place for transport, delivery, retention, retrieval, and destruction of the specimens, and will appropriately retain the specimens for up to but not longer than 15 years as required by applicable law.

Collection, Storage, and Shipment of Pharmacokinetic Samples

Instructions for processing of plasma samples for pharmacokinetic analysis of vortioxetine

1. Collect 6 mL of venous blood into a chilled Becton-Dickinson Vacutainer containing K2EDTA.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.

3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 RCF at approximately 4°C in a refrigerated centrifuge. Note: if using a collection device other than Becton-Dickinson refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number LuAA21004_402, matrix (ie, plasma), analyte (vortioxetine), Subject ID (XXXX-XXX), nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower. No more than 60 minutes will elapse between blood collection and freezing the plasma sample.
6. Keep samples frozen at approximately -20°C or lower until shipment to the central laboratory. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the central laboratory.

Shipping of plasma for vortioxetine

1. Biological samples (plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into a self-sealing bag (eg, Ziploc) containing additional absorbent material.
5. Using a permanent marker, write the subject ID, sample matrix (ie, plasma), analyte (vortioxetine), number of samples, and "SET 1" on each self-sealing bag.
6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2".
7. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (Vortioxetine), protocol number (Lu AA21004_402), investigator's name, sample type (ie, plasma), subject ID, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2". Place the

inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the central laboratory.

8. For sample packing, use dry ice generously (eg, 20 to 25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a polystyrene (eg, Styrofoam) container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the polystyrene container. Place the lid on the polystyrene container and seal completely with strapping tape. Place the polystyrene container in a cardboard shipping carton and seal securely with strapping tape.
10. Mark the outside of shipping carton(s) with a tally number (1 of 5, 2 of 5, etc).
11. Affix an address label to each shipping carton. Use the preprinted air waybills provided by the central lab.
12. Obtain the air waybill number and a receipt of shipment from the carrier.

Appendix F Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 01

Page 2, Section 1.1 Contacts

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

Change in Medical Monitor at CCI .

Page 3, Section 1.2 Approval

Existing Text

PPD

Revised Text

PPD

Change in signatory.

Page 3, Section 1.2 Approval

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

Change in signatory.

Page 18, Section 3.3 List of Abbreviations

Existing Text

No text

Revised Text

Added **CTSdatabase** to abbreviations. **Clinical Trial Subject Database (CTSdatabase)**

Rationale for Amendment

Adding vendor to the LuAA21004_402 study.

Page 18, Section 3.3 List of Abbreviations

Existing Text

HBsAG

Revised Text

HBsAg

Rationale for Amendment

Correction

Page 18, Section 3.3 List of Abbreviations

Existing Text

EDTA ethylenediaminetetraacetic acid

Revised Text

K2EDTA potassium ethylenediaminetetraacetic acid

Rationale for Amendment

Standard Takeda abbreviation.

Page 29, Section 7.2 Exclusion Criteria

Existing Text

12. The subject has a clinically significant unstable illness, for example hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, hematological, infectious, dermatological disorder or metabolic disturbance

Revised Text

12. The subject has a clinically significant unstable illness, for example hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological,

rheumatologic, immunologic, hematological, infectious, dermatological disorder or metabolic disturbance

NOTE: For the purposes of this protocol fibromyalgia, obstructive sleep apnea, chronic pain diagnosis, and morbid obesity (BMI of ≥ 40) are considered unstable due to the potential impact on assessment of the primary endpoint

Rationale for Amendment

Added clarification for unstable illnesses.

Page 30, Section 7.2 Exclusion Criteria

Existing Text

None

Revised Text

24. The subject is considered to be treatment resistant, eg, the subject has not responded to adequate monotherapy treatments of at least 6 weeks duration, or has only responded to combination or augmentation therapy

Rationale for Amendment

Provide parameters for excluding treatment resistant subjects.

Page 35, Section Criteria for Discontinuation or Withdrawal of a Subject

Existing Text

None

Revised Text

Note: A Relapse Checklist will be used by sites to evaluate potential indicators of relapse for each subject at each visit post baseline during the double blind-period.

Rationale for Amendment

Clarification of Relapse Checklist to be used by sites.

Page 41, Section 8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Existing Text

The investigator or designee must record the current inventory of all sponsor-supplied drugs (Vortioxetine 5, 10, 20 mg and placebo) on a sponsor-approved drug accountability log

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Revised Text

The investigator or designee must record the current inventory of all sponsor-supplied drugs (Vortioxetine 5, 10, 20 mg and placebo) on a sponsor-approved drug accountability log/**IWRS**.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log/**IWRS.**

Rationale for Amendment

IWRS will capture all drug accountability for this study.

Page 42, Section 9.1.1.2 Clinical Trial Subject Database (CTSdatabase) Authorization

Existing Text

None

Revised Text

A separate subject authorization will be obtained at the Screening Visit that will allow sites to enter specific subject information into CTSdatabase, a clinical trial registry.

Rationale for Amendment

Subject authorization is needed for CTSdatabase to be able to use the subject's information.

Page 42, Section 9.1.2 CTSdatabase and Subject Database Authorization

Existing Text

None

Revised Text

Clinical trial registries, such as CTSdatabase, seek to reduce subjects from enrolling into multiple clinical trials by identifying duplicates before enrollment. At the time of providing the informed consent for the study, the Investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

During screen, site staff that have received training and login information access www.ctsdatabase.com and enter the subject study ID and authorized subject identifiers. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days or (3) the subject matches with a subject who has pre-screened at another site.

Rationale for Amendment

Adding vendor CTSdatabase to help reduce the potential for subjects to participate in multiple trials simultaneously.

Page 43, Section 9.1.6 Vital Sign Procedure

Existing Text

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw

Revised Text

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained before or after the scheduled blood draw.

Rationale for Amendment

Clarification on when to take vital signs.

Page 44, Section 9.1.8 Primary Efficacy Measurements

Existing Text

MADRS

Revised Text

Prompted MADRS

Rationale for Amendment

Clarification.

Page 46, Section Table 9.a Clinical Laboratory Tests

Existing Text

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.2 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

The abnormality should be recorded as an AE (please refer to Section 10.2.2 Reporting of Abnormal Liver Function Tests for reporting requirements).

Revised Text

(Please refer to Section 7.5 for discontinuation criteria, and Section **10.1.5.2** for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

The abnormality should be recorded as an AE (please refer to Section **10.2.1.3** Reporting of Abnormal Liver Function Tests for reporting requirements).

Rationale for Amendment

Correct reference sections added.

Page 49, Section 9.1.16 Pharmacogenomic Sample Collection

Existing Text

Two 3-mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day 1 from each subject in the study, into plastic K2 ethylenediaminetetraacetic acid (EDTA) spray-coated tubes, and stored under frozen conditions.

Two whole blood samples (2.5 mL per sample) will be collected at each time point at predose on Day 1, Week 8, Week 16 and Week 48 for ribonucleic acid (RNA) pharmacogenomic analysis from each subject in the study, into a PaxGene ™ tube.

Revised Text

Two 3-mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day **0** from each subject in the study, into plastic potassium ethylenediaminetetraacetic acid (**K2**EDTA) spray-coated tubes, and stored under frozen conditions.

Two whole blood samples (2.5 mL per sample) will be collected at each time point at predose on Day **0**, Week 8 **(Visit 6),** Week 16 **(Visit 10)** and Week 48 **(Completion/Early Termination**) for ribonucleic acid (RNA) pharmacogenomic analysis from each subject in the study, into a PaxGene ™ tube. **For subjects who withdraw during the open-label treatment period, a blood sample will be collected at study termination, regardless of the treatment duration.**

Rationale for Amendment

Corrected day 1 to accurately reflect day 0. Added visit numbers for consistency. Added blood sample for any early withdrawal visit during open-label. Corrected abbreviation.

Page 50, Section 9.1.17.1 Collection of Plasma for Pharmacokinetic Sampling

Existing Text

None

Revised Text

For subjects who withdraw during the open-label treatment period, blood samples will be collected at study termination, regardless of the treatment duration.

Rationale for Amendment

Added blood sample for any early withdrawal visit during open-label.

Page 50, Section 9.1.17.1 Collection of Plasma for Pharmacokinetic Sampling

Existing Text

Following randomization on week 16, 2 additional blood samples from each subject will be collected at Week 32 (Visit 15) and Week 48 (Completion)/Early Termination.

Revised Text

Following randomization on **W**eek 16 **(Visit 10)**, 2 additional blood samples from each subject will be collected at Week 32 (Visit 15) and Week 48 (Completion)/Early Termination.

Rationale for Amendment

Capitalized week. Added visit number for consistency.

Page 52, Section 9.1.21.1 Prior to Study Start

Existing Text

NOTE: The investigator (MD or DO ie, a physician) responsible for the subject must be the only one to rate the subject using the CGI-S.

Revised Text

Note: The investigator responsible for the subject must be the only one to rate the subject using the CGI. The investigator is defined as a clinician with suitable training and experience as deemed by the sponsor.

Rationale for Amendment

Clarified definition of rater qualification for CGI.

Page 54, Section 9.3.1 Screening Visit 1 (Days -21 to -5)

Existing Text

Sites will complete a pre-randomization form for subjects who meet the screening requirements.

Revised Text

Sites will complete a **pre-enrollment** form for subjects who meet the screening requirements.

Rationale for Amendment

Changed to reflect that this form is completed prior to enrollment.

Page 54, Section 9.3.1 Screening Visit 1 (Days -21 to -5)

Existing Text

None

Revised Text

CTSdatabase Authorization

Rationale for Amendment

Added procedure to obtain authorization from subject for CTSdatabase.

Page 54, Section 9.3.1 Screening Visit 1 (Days -21 to -5)

Existing Text

MADRS

Revised Text

Prompted MADRS

Rationale for Amendment

Clarification.

Page 55, Section 9.3.2 Study Entrance into Open-Label Treatment; Baseline I, Visit 2 (Day 0)

Existing Text

Subjects will be instructed on when to take the first dose of investigational drug as described in Section 6.1.

Revised Text

Subjects will be instructed on when to take the first dose of investigational drug as described in Section **8.1.3**.

Rationale for Amendment

Correct reference section added.

Page 56, Section 9.3.4 Withdrawal Visit from Open-label Treatment (± 3 days)

Existing Text

This visit will be performed for any subject that does not meet response or remission criteria during open-label period or has met other withdrawal criteria outlined in Section 7.7.

Revised Text

This visit will be performed for any subject that does not meet response or remission criteria during open-label period or has met other withdrawal criteria outlined in Section **7.5**.

Rationale for Amendment

Correct reference section added.

Page 56, Section 9.3.4 Withdrawal Visit from Open-label Treatment (± 3 days)

Existing Text

None

Revised Text

- **PK sampling for study medication**
- **Pharmacogenomic sampling RNA**

Rationale for Amendment

Added blood samples for PK and RNA for any open-label treatment withdrawal.

Pages 58-59, Sections 9.3.6, 9.3.8 and 9.3.9

Existing Text

None

Revised Text

Relapse Checklist

Rationale for Amendment

Added to ensure that sites are completing the Relapse Checklist at each double-blind treatment visit.

Page 58, Section 9.3.7 Double-Blind Treatment Subject Well Being Calls Weeks 22, 26, 30, 34, 38, 42, and 46

Existing Text

Double-Blind Treatment Subject Well Being Calls Weeks 22, 26, 30, 34, 38, and 42

Revised Text

Double-Blind Treatment Subject Well Being Calls Weeks 22, 26, 30, 34, 38, 42, **and 46**

Rationale for Amendment

Added week 46 for consistency with protocol.

Page 59, Section 9.3.9 Completion/Withdrawal from Double-Blind, Visit19, Week 48 (± 5 days)

Existing Text

This visit will be performed for any subject who relapses during double-blind period or has met other withdrawal criteria outlined in Section 7.7.

Revised Text

This visit will be performed for any subject who relapses during double-blind period or has met other withdrawal criteria outlined in Section**7.5**

Rationale for Amendment

Correct reference section added.

Page 64, Section 10.1.4 SAEs

Existing Text

Leads to a CONGENITAL ANOMALY/BIRTH DEFECT

Revised Text

Is a CONGENITAL ANOMALY/BIRTH DEFECT

Rationale for Amendment

Required change per Takeda template.

Page 83, Section Appendix A Schedule of Study Procedures

Existing Text

None

Revised Text

CTSdatabase added at Screening Visit

PK sampling for study medications added at withdrawal visit

Pharmacogenomic sampling added at withdrawal visit

Rationale for Amendment

Subject authorization needed for CTSdatabase.

Decision to obtain PK and RNA sample at any open-label withdrawal visit.

Page 83-86, Section Appendix A Schedule of Study Procedures

Existing Text

(a) All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible.
(b) Update at Baseline I.
(c) Subjects must meet response criteria from Week 8 through Week 16 and remission criteria at Weeks 14 and 16.
(d) Pretreatment event assessment occurs from the date of Screening up to the first dose of study medication.
(e) Assess post-treatment adverse events, ongoing adverse events and/or serious adverse events, and record all ongoing medications for subjects who withdraw early.
(f) Fasting labs must be performed at Baseline I and Baseline II (randomization).
(g) Serum hCG for female subject of childbearing potential at Screening, Baseline II (randomization) and Withdrawal. Urine stick pregnancy tests to be done at all other visits.
(h) The sample for pharmacogenomics may be drawn at the earliest visit after Baseline I, if missed at visit 2 (Baseline I). Pharmacogenomics sample collection is optional for subjects. A separate Informed Consent Form will be obtained. Only RNA pharmacogenomic sample collected on Week 8 and Week 16 visit.
(i) The subjects will be instructed to take the first dose of study medication on the morning after enrollment (Baseline I).

Revised Text

(a) Subjects who meet all randomization criteria please follow schedule of procedures for week 16 on schedule of study procedures for double-blind treatment period.
(b) All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible.
(c) Obtain subject authorization, enter subject into the CTS database.
(d) Update at Baseline I.
(e) Subjects must meet response criteria from Week 8 through Week 16 and remission criteria at Weeks 14 and 16.
(f) Pretreatment event assessment occurs from the date of Screening up to the first dose of study medication.
(g) Assess post-treatment adverse events, ongoing adverse events and/or serious adverse events, and record all ongoing medications for subjects who withdraw early.
(h) Fasting labs must be performed at Baseline I and Baseline II (randomization).
(i) Serum hCG for female subject of childbearing potential at Screening, Baseline II (randomization) and Withdrawal. Urine stick pregnancy tests to be done at all other visits.
(j) Two whole blood samples (3 mL per sample) will be collected predose on Day 0 for DNA isolation. Two whole blood samples (2.5 mL per sample) will be collected for RNA isolation at each time point at predose on Day 0 and weeks 8, and 16 and any early withdrawal visit during open-label. The sample for pharmacogenomics may be drawn at the earliest**.**
(k) The subjects will be instructed to take the first dose of study medication on the morning after enrollment (Baseline I).

Rationale for Amendment

Clarification for procedures at week 16 for subjects who are randomized.

Addition of subject authorization for CTSdatabase.

Clarification for PGx blood draws during the open-label period.

Page 86, Section Appendix A Schedule of Study Procedures

Existing Text

None

Revised Text

Relapse Checklist added at visits 18-48

Rationale for Amendment

Added to ensure sites are completing checklist at these visits.

Page 86, Section Appendix A Schedule of Study Procedures

Existing Text

(a) Subject well-being phone calls should be made every 2 weeks post Week 20.

Revised Text

(a) Subject well-being phone calls should be made every 2 weeks post Week 20 **through Week 46**

Rationale for Amendment

Consistency with the protocol.

Page 86, Section Appendix A Schedule of Study Procedures

Existing Text

(g) PK sampling must be taken prior to first dose of double-blind study medication. If subject is not randomized, PK sample should still be drawn. Collect only one PK sample at Week 16 draw

Revised Text

(g) **PK sampling must be taken prior to first dose of double-blind study medication.**

Rationale for Amendment

Deleted part of footnote instructions for consistency with schedule of procedures for open-label treatment period.

Page 93, Section Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Existing Text

None

Revised Text

For subjects who withdraw during the open-label treatment period, a blood sample will be collected at study termination, regardless of the treatment duration

Rationale for Amendment

Added PK sample for any early withdrawal visit during open-label treatment.

Page 94, Section Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Existing Text

A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number Lu AA21004_402, matrix (ie, plasma), analyte (vortioxetine), enrollment number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).

Revised Text

A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number Lu AA21004_402, matrix (ie, plasma), analyte (vortioxetine), **Subject ID (XXXX-XXX),** nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).

Rationale for Amendment

Clarification of enrollment number as the Subject ID.

Page 94, Section Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Existing Text

Keep samples frozen at approximately -20°C or lower until shipment to the analytical laboratory. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory

SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.

Revised Text

Keep samples frozen at approximately -20°C or lower until shipment to the central laboratory. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the **central** laboratory

SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the **central** laboratory

Rationale for Amendment

Corrected to show analytical lab as the central lab.

Page 94, Section Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Existing Text

Using a permanent marker, write the 4-digit subject number, sample matrix (ie, plasma, urine), analyte (vortioxetine), number of samples, and "SET 1" on each self-sealing bag

An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (Vortioxetine), protocol number (Lu AA21004_402), investigator's name, sample type (ie, plasma), 4-digit enrollment number, nominal collection day and time, and intended sample storage conditions.

Revised Text

Using a permanent marker, write the **subject ID**, sample matrix (ie, plasma), analyte (vortioxetine), number of samples, and "SET 1" on each self-sealing bag

An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (Vortioxetine), protocol number (Lu AA21004_402), investigator's name, sample type (ie, plasma), **subject ID**, nominal collection day and time, and intended sample storage conditions.

Rationale for Amendment

Corrected to indicates subject ID and removed urine as a sample.

Page 95, Section Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Existing Text

Affix an address label to each shipping carton.

Revised Text

Affix an address label to each shipping carton. **Use the preprinted air waybills provided by the central lab**

Rationale for Amendment

Instructions for sites to use preprinted air waybills.

Page 95, Section Collection, Shipment, and Storage of Pharmacogenomic and Collection, Storage, and Shipment of PK Samples

Existing Text

Obtain the airway bill number and a receipt of shipment from the carrier

Revised Text

Obtain the **air waybill** number and a receipt of shipment from the carrier

Rationale for Amendment

Minor typo.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Biostatistics Approval	29-Sep-2015 13:25
	Clinical Operations Approval	29-Sep-2015 14:55
	Clinical Science Approval	29-Sep-2015 19:37