Title: An Open-Label, Single-Arm, Multicenter, Prospective, Phase 4, Interventional, Flexible Dose Study to Evaluate the Effectiveness of Vortioxetine on Goal Achievement After a Change in Antidepressant Medication for the Treatment of Subjects With Major Depressive Disorder

NCT Number: NCT02972632

Protocol Approve Date: 18 August 2017

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 or company confidential information.

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.

TAKEDA PHARMACEUTICALS

PROTOCOL AMENDMENT

An Open-Label, Single-Arm, Multicenter, Prospective, Phase 4, Interventional, Flexible Dose Study to Evaluate the Effectiveness of Vortioxetine on Goal Achievement After a Change in Antidepressant Medication for the Treatment of Subjects With Major Depressive Disorder

Goal Achievement After a Change to Vortioxetine in Adults With Major Depressive Disorder

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015		
Study Number:	Vortioxetine-4003		
IND Number:	76,307	**EudraCT Number:**	N/A
Compound:	Vortioxetine		
Date:	18 August 2017	**Version/Amendment Number:**	1

Amendment History:

Date	Amendment Number	Amendment Type	Region
30 August 2016	Initial version	Not applicable	Global
18 August 2017	01	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center (TDC) 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	US Contact
Serious adverse event and pregnancy reporting	Personal Protected Data
Medical Monitor (medical advice on protocol and study drug)	
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 study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6(R2) 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 are provided on the last page of this document.

1.3 Protocol Amendment #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 responsible medical officer contact, clarify Exclusion Criteria #4, Company Confidential Information, add assessment of GAS approach, and revise interim analysis criteria. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only. Full details regarding the text changes are given in Appendix E, including detailed rationale. The following is a summary of the changes made in the amendment:

- Updated responsible medical officer and protocol signatories.
  - Justification: Change in personnel.
- Clarified Exclusion Criteria #4.
  - Justification: The intent of this criteria is to exclude subjects who currently have significant risk of suicide (according to the investigator's clinical judgment), or made an actual suicide attempt in the previous 6 months prior to Screening, or within the same time frame have had active suicidal ideation with some intent to act (item 4 of CSSRS) or have had active suicidal ideation with specific plan and intent to act (item 5 of CSSRS). A lifetime "yes" answer to items 4 and 5 will not exclude the subject, but a "yes" answer to past 6 months for items 4 and 5 is exclusionary.
- Added assessment of Clinician and subject satisfaction with the GAS approach as a method for establishing treatment goals, evaluating progress towards treatment goals, and improving communication between clinicians and patients.
  - Justification: To assess the GAS approach in clinical practice and to guide future GAS work.
- Company Confidential Information.
  - Company Confidential Information
- Clarified Interim Analysis criteria.
  - Justification: Analysis will be conducted once 60 subjects have completed, but enrollment will not be stopped.
- Correction of inconsistencies within the original protocol.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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 Council for Harmonisation, E6(R2) 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 study site agreement.
- Responsibilities of the Investigator. (Appendix B)

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)

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="3">Name of Sponsor:
Takeda Development Center Americas, Inc.</td><td colspan="3">Compound:
Vortioxetine</td></tr>
<tr><td colspan="4">Title of Protocol: An Open-Label, Single-Arm, Multicenter, Prospective, Phase 4, Interventional, Flexible Dose Study to Evaluate the Effectiveness of Vortioxetine on Goal Achievement After a Change in Antidepressant Medication for the Treatment of Subjects With Major Depressive Disorder</td><td colspan="2">IND No.: 76,307</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td colspan="4">Study Number: Vortioxetine-4003</td><td colspan="2">Phase: 4</td></tr>
<tr><td colspan="6">Study Design:
This study is a nonrandomized, open-label, single-arm, multicenter, prospective, phase 4, interventional, flexible-dose study to determine the effectiveness of treatment with vortioxetine (per Trintellix United States [US] package insert) on subject goal achievement after a change in antidepressant medication for the treatment of major depressive disorder (MDD).
Potential subjects with MDD who are changing from another antidepressant to vortioxetine per routine care will be eligible to enroll. Subjects will determine treatment goals with their clinicians utilizing the Goal Attainment Scale (GAS) Methodology adapted for an MDD population. The subject and clinician will work to establish 3 goals at Baseline. One goal will be determined based on the subject's self-defined objectives. Two goals will be selected from the following predefined categories representing MDD residual symptoms, antidepressant side effects, and common reasons for changing antidepressant medication, including but not limited to:</td></tr>
<tr><td>MDD Domains</td><td>Psychological</td><td>Motivation</td><td>Emotional</td><td>Physical/ Functional</td><td>Cognition</td></tr>
<tr><td>Predefined Goal Categories:</td><td>Depressed mood Anxious mood</td><td>Lack of motivation</td><td>Low self esteem Anhedonia</td><td>Fatigue
Insomnia
Muscle tension
Sexual dysfunction
Weight gain</td><td>Problems concentrating
Short-term memory problems
Difficulty staying focused
Difficulty paying attention
Problems thinking clearly</td></tr>
<tr><td colspan="6">This study is comprised of up to a 3-week Screening Period, followed by a 12-week Treatment Period and a 4-week Safety Follow-up Period. Study visits will occur at Baseline (Day 1), and Weeks 2, 4 (Telephone), 6, 9 (Telephone), and 12. This study will enroll approximately 120 subjects and will be conducted at approximately 25 sites in the United States. The investigator or the investigator's designee will access the Interactive Response Technology (IxRT) at Screening to obtain the subject study number. At the Baseline Visit, if the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for enrollment, the subject will be enrolled using the IxRT. Subjects will be instructed on when to take the first dose of study drug. The dosing (both initial and adjustments) will be determined by the investigator or designee as per routine clinical practice and per approved Trintellix labeling.
Subjects who discontinue or who are withdrawn prior to study completion will come to the site for an Early Termination Visit as soon as possible and will be contacted for a Safety Follow-up 4 weeks after the last dose of study medication.
A futility analysis may be performed at an interim analysis after approximately 60 subjects have completed the study.</td></tr>
</table>

Primary Objective:

To determine the effectiveness of treatment with vortioxetine on subject goal achievement after a change in antidepressant medication for the treatment of MDD.

Secondary Objectives:

To determine the effectiveness of treatment with vortioxetine on depressive symptoms/outcomes, clinical global impression, cognitive impairment, and quality of life in subjects with MDD.

Exploratory/Additional Objectives:

- To determine the effectiveness of treatment with vortioxetine on cognitive performance and functionality in subjects with MDD.
- To determine the effectiveness of treatment with vortioxetine on work performance in subjects with MDD.
- To determine the effectiveness of treatment with vortioxetine on general health status and well being in subjects with MDD.
- To assess health care utilization and the safety and tolerability of vortioxetine in subjects with MDD.

Safety Assessments

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

- Adverse events (AEs).
- AEs leading to discontinuation.
- Weight.
- Columbia-Suicide Severity Rating Scale (C-SSRS).

Subject Population: Men and women between the ages of 18 and 65 years, inclusive, with a primary diagnosis of MDD, who have previously been treated within 6 weeks of Screening or are currently being treated for a major depressive episode (MDE) with an approved antidepressant for 6 weeks or longer at an adequate dose. The change in antidepressant medication will be based on the investigator's judgment in collaboration with the subject's level of dissatisfaction with their current or recent antidepressant treatment (ie, residual mood symptoms, intolerable side effects). Subjects currently on an antidepressant at Screening will be discontinued in a manner that is consistent with labeling recommendations and conventional medical practice. Enrollment caps may be implemented throughout the course of the study based on the patient reported outcome (ie, Patient Health Questionnaire-9 [PHQ-9] and Perceived Deficits Questionnaire-Depression [PDQ-D]) scores at Baseline.

Number of Subjects: Approximately 120 subjects	**Number of Sites:** Estimated total: approximately 25 sites in the United States
Dose Levels: Vortioxetine 5, 10, or 20 mg once daily as per Trintellix US Package Insert	**Route of Administration:** Oral
Duration of Treatment: 12-week Treatment Period	**Period of Evaluation:** Up to 19 weeks including a 3-week Screening Period (maximum of 21 days), a 12-week Treatment Period and 4-week Safety Follow-up Period

Main Criteria for Inclusion:

1. Subject is a man or woman between 18 to 65 years, inclusive, and able to read and understand English.
2. Subject suffers from MDD as the primary psychiatric diagnosis.
3. Subject has been or is currently being treated with an approved antidepressant (monotherapy) for 6 weeks or longer at an adequate therapeutic dose as per investigator judgment.
4. The antidepressant treatment must be ongoing or have been discontinued within 6 weeks of Screening. Subjects currently on an antidepressant at Screening will be discontinued in a manner that is consistent with labeling recommendations and conventional medical practice.
5. Subject is considered appropriate for a change in antidepressant medication based on investigator judgment in collaboration with the subject.
6. Subject has scores on PHQ-9 ≥5 and Clinical Global Impression Scale-Severity (CGI-S) ≥4 at Screening.
7. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
8. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
9. A female subject of childbearing potential who is sexually active 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 of study drug.

Main Criteria for Exclusion:

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

1. Subject has any current psychiatric disorder other than MDD (except nonprimary concurrent anxiety), other illness or condition which may compromise the study in the opinion of the investigator.
2. The subject has discontinued prior antidepressant treatment greater than 6 weeks prior to Screening.
3. Subject is considered to be at imminent risk for hospitalization due to severe depression in the opinion of the investigator. Recent hospitalization due to MDD within 3 months prior to Screening is also exclusionary.
4. The subject has a significant risk of suicide according to the investigator's clinical judgment or has made an actual suicide attempt in the previous 6 months prior to Screening or scores "yes" on Items 4 or 5 in the past 6 months on the Suicidal Ideation section of the C-SSRS.
5. The subject is considered to be treatment resistant, defined as patients with MDD who have not responded to 2 or more different antidepressants monotherapy studies of adequate dose and duration (6 weeks or longer) in their current episode. History of only responding to either combination or augmentation therapy in previous MDEs is also considered evidence of treatment resistant depression.
6. The subject has received any investigational compound within 30 days prior to Screening or 5 half-lives prior to Screening, whichever is longer.
7. The subject has previously or is currently participating in this study or another vortioxetine or LuAA21004 study.
8. The subject has participated in 2 or more interventional clinical studies in the year prior to Screening, or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol.
9. 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).
10. The subject has 1 or more of the following:
    a) 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, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in The Diagnostic and Statistical Manual of Mental Disorders,

Fifth Edition as determined by the investigator.

b) Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine). The subject must have a negative urine drug screen at Screening and Baseline, this includes benzodiazepines and opiates (including oxycodone) for which there is no prescription.

c) Presence or history of a clinically significant neurological disorder (including epilepsy) as determined by the investigator.

d) Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc).

11. The subject has received vortioxetine previously, or the subject has a history of hypersensitivity or allergies to vortioxetine or any of its components.
12. Subjects receiving or who have started receiving formal cognitive or behavioral therapy, systematic psychotherapy within 30 days from screening or plan to initiate such therapy during the study (marital therapy, and bereavement counseling are allowed).
13. The subject is receiving excluded medications or it is anticipated that the subject will require treatment with at least 1 of the disallowed concomitant medications during the study.
14. The subject has a clinically significant unstable illness as determined by the investigator.
15. The subject has a known history of acute narrow-angle glaucoma or is at risk of acute narrow-angle glaucoma.
16. The subject has a known unstable thyroid disorder or a thyroid-stimulating hormone value outside the normal range based on medical history that is deemed clinically significant by the investigator.
17. The subject has clinically significant abnormal vital signs as determined by the investigator.
18. The subject has active hepatitis B or a known history of hepatitis C virus.
19. The subject has a known history of human immunodeficiency virus infection.
20. The subject has a history of gastric bypass.
21. The subject has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or effectiveness.
22. 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.

Main Criteria for Evaluation and Analyses:

- **Primary endpoint**: Proportion of subjects who achieve their identified goals as demonstrated by an outcome GAS Score of $\geq$50 at Week 12.
- **Secondary endpoints**:
  - Mean change from Baseline in total GAS Score at Week 6 and Week 12.
  - Change from Baseline in depression severity as measured by the PHQ-9 Score at Week 6 and 12.
  - Change from Baseline in perceived cognitive deficits and cognitive function as measured by the PDQ-D at Weeks 6 and 12.
  - Change from Baseline in Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q) Score at Week 12.
  - Change from Baseline in 5-item World Health Organization Well-Being Index (WHO-5) Score at Week 12.
  - Change from Baseline in CGI-S at Week 12.
  - Clinical Global Impression Scale-Improvement (CGI-I) Score at Week 12.

- **Exploratory/Additional**:

Company Confidential Information

[redacted]

Safety Assessments

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

- AEs.
- AEs leading to discontinuation.
- Weight.
- C-SSRS.

Statistical Considerations:

Primary Effectiveness Analysis:

- The primary effectiveness variable will be the proportion of subjects who changed to treatment with vortioxetine who achieve their identified goals at Week 12 (ie, GAS Score ≥50). The GAS yields a norm-based score (standardized to a mean of 50, SD of 10) at Baseline and for each follow-up; the change from score at Baseline will be summarized. The responder rate at Week 12 and the change in total GAS Score at each follow-up will be assessed by the 95% CI. Similar analyses will be done for other endpoints.

Secondary Effectiveness Analysis:

A paired t-test will be applied to the change from Baseline for the GAS Score. For the secondary endpoints of outcomes measures on PHQ-9, PDQ-D, Q-LES-Q Score, WHO-5 Score, and CGI-S total scores and changes from Baseline will be summarized by each time point of Baseline and Week 12 with paired t-tests. Tests of significance will be 2-tailed with alpha level at 0.05. CGI-I Scores will be summarized at Week 12 using descriptive statistics.

Additional analyses:

Company Confidential Information

[redacted]

Safety Analysis:

The safety data will be summarized. AEs will be reported throughout the study. The definition of treatment-emergent AEs will be provided in the statistical analysis plan. AEs will be coded using the Medical Dictionary for Regulatory Activities and will be summarized by system organ class and preferred term. AEs 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.

Sample Size Justification:

As no formal hypothesis testing is performed for the primary endpoint, the purpose of sample size estimation is to determine the adequate sample size needed to provide a precise estimate for the response rate (GAS Score ≥50) with 95% CIs. Conservatively estimating that 50% of subjects will be responders (GAS ≥50) and that 100 subjects will complete the study, CIs will be ±0.098 around the point estimate (proportion of responders).

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. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating 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 drug, 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

5-HT	serotonin
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CGI-I	Clinical Global Impression Scale-Improvement
CGI-S	Clinical Global Impression Scale-Severity
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DRESS	drug reaction with eosinophilia and systemic symptoms
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FSH	follicle-stimulating hormone
GAS	Goal Attainment Scale
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IxRT	Interactive Response Technology
LFT	liver function tests
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
PGx	pharmacogenomics
PDQ-D	Perceived Deficits Questionnaire-Depression
PHQ-9	Patient Health Questionnaire-9
PPS	per protocol set
PTE	pretreatment event
Q-LES-Q	Quality of Life and Enjoyment and Satisfaction Questionnaire
QD	once daily
SAE	serious adverse event
SJS	Stevens-Johnson syndrome

STAR*D	Sequenced Treatment Alternatives to Relieve Depression
SUSAR	suspected unexpected serious adverse reaction
TEN	toxic epidermal necrolysis
UDS	urine drug screen
ULN	upper limit of normal
US	United States
Company Confidential Information	Company Confidential Information
WAIS-IV	Wechsler Adult Intelligence Scale Fourth Edition
WHO	World Health Organization
WHO-5	5-item World Health Organization Well-Being Index

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
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

According to the World Health Organization (WHO), depression 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) [1]. Specifically in the United States, the prevalence of major depressive disorder (MDD) is currently 8.3%, with expectations that prevalence will increase over the coming years [2].

The economic consequences of MDD are significant. The ability of depressed patients or their caregivers to work and make productive contributions to the economy is reduced, while the use of treatment and support services is increased. 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 [1].

Depression is recurrent in 75% to 80% of patients and becomes chronic (lasts 2 years or longer) in 15% to 20% of depressed patients [3,4]. Furthermore, depression can lead to substantial impairments in an individual's ability to take care of his/her everyday responsibilities and approximately 15% of depressed patients commit suicide [5]. Unfortunately, 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 continued treatment to prevent relapse and recurrence are both major priorities for management of recurrent MDD [6,7].

4.1.1 Vortioxetine

Vortioxetine 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-HT3, 5-HT7, and 5-HT1D receptors, an agonist at 5-HT1A receptors, a partial agonist at 5-HT1B receptors, and an inhibitor of the 5-HT transporter [8,9]. The following sections briefly review the results from nonclinical and clinical studies of vortioxetine.

4.1.1.1 Nonclinical Background

Preclinical studies concluded that vortioxetine had a difference pharmacological profile than other selective serotonin reuptake inhibitors) and serotonin noradrenaline reuptake inhibitors. Key pharmacological differences include its interaction with 5-HT targets which modulates multiple neurotransmitter systems, the reversal of cognitive deficits in various animal models, and its effects in depression models [10].

4.1.1.2 Clinical Background

During the clinical development program, the efficacy, safety, and tolerability of vortioxetine in MDD subjects was evaluated at doses from 1 to 20 mg once daily (QD) in short-term efficacy

studies of 6 to 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 6- to 8-week randomized, double-blind, placebo-controlled, fixed-dose studies (including 1 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 [11].

4.2 Rationale for the Proposed Study

After unsuccessful treatment with initial antidepressant monotherapy treatment of adequate dose and duration, clinical practice guidelines for the treatment of MDD recommend changing the antidepressant. This treatment change may be necessary when patients respond poorly to antidepressant medication or exhibit intolerable side effects.

Data from clinical studies regarding switching antidepressant medication rates is minimal and the rationale for the switch varies across studies [12]. Claims databases have shown switching rates for antidepressants have ranged from 2.78% to 13.7% [13,14]. The results of switching, in particular, multiple switching can lead to suboptimal outcomes for patients. Results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that as the number of switches increased the burden of illness, including relapse rates, also increased. Relapse may trigger a pharmacologic switch [15]. Switching antidepressant agents has been shown to increase treatment costs and can be burdensome to the patient, so it is important to get the patient to the optimal treatment as early as possible in the therapeutic pathway [16].

A process used in the mental health arena to assess and capture the patient's experience regarding whether or not treatment is successful is Goal Attainment Scaling; however, this approach has not been widely used in assessing the treatment of depression or in clinical research. Goal Attainment Scaling was first developed by Thomas Kiresuk and Robert Sherman in response to the wide variety of evaluation models regarding mental illness and treatment [17]. Goal Attainment Scaling has long been used in clinical care and program assessment to evaluate patient progress and ensure alignment between clinician and patient on treatment objectives [17]. Through a structured interview and goal setting between clinician and patient, the Goal Attainment Scaling process captures meaningful aspects of a person's progress throughout the course of treatment that are challenging to assess using available standardized measures. The aim of this study is to demonstrate that the process of Goal Attainment Scaling in MDD in conjunction with a change in antidepressant treatment to vortioxetine is effective in achieving outcomes that matter to patients, improves quality of life and is an effective strategy to treat MDD when the current or recent antidepressant is not adequate.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To determine the effectiveness of treatment with vortioxetine on subject goal achievement after a change in antidepressant medication for the treatment of MDD.

5.1.2 Secondary Objectives

To determine the effectiveness of treatment with vortioxetine on depressive symptoms/outcomes, clinical global impression, cognitive impairment, and quality of life in subjects with MDD.

5.1.3 Additional Objectives

- To determine the effectiveness of treatment with vortioxetine on cognitive performance and functionality in subjects with MDD.
- To determine the effectiveness of treatment with vortioxetine on work performance in subjects with MDD.
- To determine the effectiveness of treatment with vortioxetine on general health status and well being in subjects with MDD.
- To assess health care utilization and the safety and tolerability of vortioxetine in subjects with MDD.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is to estimate the proportion of subjects who achieve their identified goals as demonstrated by an outcome Goal Attainment Scale (GAS) Score of $\geq$50 at Week 12.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- Mean change from Baseline in total GAS Score at Week 6 and Week 12.
- Change from Baseline in depression severity as measured by the Patient Health Questionnaire (PHQ-9) Score at Weeks 6 and 12.
- Change from Baseline in perceived cognitive deficits and cognitive function as measured by the Perceived Deficits Questionnaire-Depression (PDQ-D) at Weeks 6 and 12.
- Change from Baseline in Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q) Score at Week 12.

- Change from Baseline in 5-item World Health Organization Well-Being Index (WHO-5) Score at Week 12.
- Change from Baseline in Clinical Global Impression Scale Severity (CGI-S) at Week 12.
- Clinical Global Impression Scale-Improvement (CGI-I) Score at Week 12.

5.2.3 Additional Endpoints

The exploratory/additional endpoints include:

5.3 Safety Assessments

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

- Adverse events (AEs).
- AEs leading to discontinuation.
- Weight.
- Columbia-Suicide Severity Rating Scale (C-SSRS).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This study is an open-label, single-arm, multicenter, prospective, phase 4, interventional, flexible-dose study (as per the Trintellix US package insert) to determine the effectiveness of treatment with vortioxetine on subject goal achievement after a change in antidepressant medication for the treatment of MDD.

This study is comprised of a 3-week Screening Period (maximum 21 days), to be followed by a 12-week Treatment Period and a 4-week Safety Follow-up Period. Study visits will occur at Baseline (Day 1), and Weeks 2, 4 (Telephone), 6, 9 (Telephone), and 12. This study will enroll approximately 120 subjects and will be conducted at approximately 25 sites in the United States.

This study will enroll men and women between the ages of 18 and 65, inclusive, with a primary diagnosis of MDD, who have previously been treated within 6 weeks of Screening or are currently being treated for a major depressive episode (MDE) with an approved antidepressant for 6 weeks or longer at an adequate dose. Subjects who are dissatisfied with their current or recent antidepressant and are interested in a change in antidepressant treatment will be eligible for Screening.

The change in antidepressant medication will be based on the investigator's judgment in collaboration with the subject's level of dissatisfaction with their current or recent antidepressant treatment (ie, residual mood symptoms, intolerable side effects). Subjects also need to be eligible per the Trintellix United States (US) package insert and sign and date a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.

The investigator or the investigator's designee will access the Interactive Response Technology (IxRT) at Screening to obtain the subject study number. At the Baseline Visit, if the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for enrollment, the subject will be enrolled using the IxRT. Subjects will be instructed on when to take the first dose of study drug. The dosing (both initial and adjustments) will be determined by investigator or designee as per routine clinical practice and per approved Trintellix labeling. Subjects will determine treatment goals with their clinicians using the GAS adapted for an MDD population. The subject and clinician will work to establish 3 goals at Baseline. One goal will be determined based on the subject's self-defined objectives. Two goals will be selected from the following predefined categories representing MDD residual symptoms, antidepressant side effects, and common reasons for a change in antidepressant medication, including but not limited to:

MDD Domains	Psychological	Motivation	Emotional	Physical/ Functional	Cognition
Predefined goal categories:	-Depressed mood -Anxious mood	-Lack of motivation	-Low self esteem -Anhedonia	-Fatigue -Insomnia -Muscle tension -Sexual dysfunction -Weight gain	-Problems concentrating -Short term memory problems -Difficulty staying focused -Difficulty paying attention -Problems thinking clearly

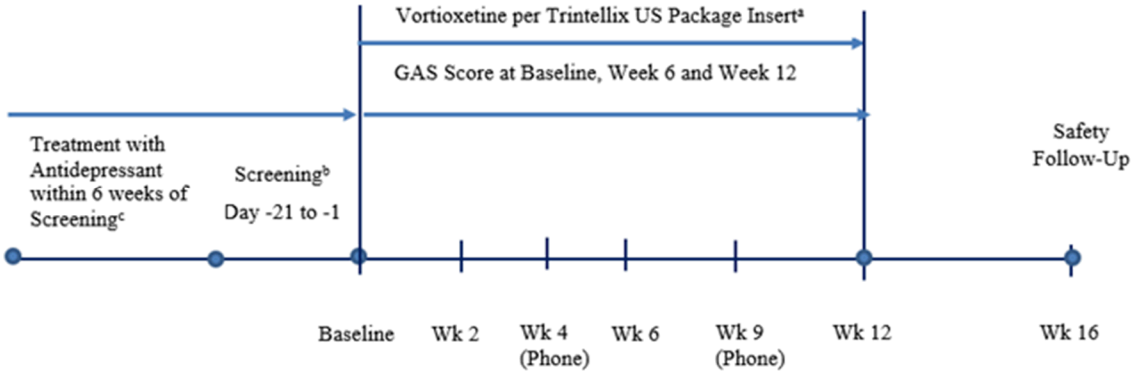
A prepopulated list of categories will be provided in the structured guidance for goal assessment, including behavioral examples describing goals and observable benchmarks to help clinicians set the appropriate goals with subjects. Goals will be set at Baseline/Visit 1. Progress will be evaluated at the Week 6 visit. At the Final Visit the goals will be assessed based on levels of achievement on a 5-point scale. Investigators will be trained on goal setting/goal assessment and monitored for ability in key domains of goal setting (eg, attainability of goals, use of observable objectives and benchmarks, equidistance of scaling, general level of difficulty, goal differentiation, and overall quality).

A safety follow-up phone call will be made 4 weeks after completion of the 12 weeks of treatment. Subjects who discontinue or who are withdrawn prior to study completion will come to the site for an Early Termination Visit as soon as possible and will be contacted for a safety follow-up 4 weeks after the last dose of study medication.

Enrollment caps may be implemented throughout the course of the study based on the patient reported outcome (ie, PHQ-9 and PDQ-D) scores at Baseline.

A futility analysis may be performed at an interim analysis after approximately 60 subjects have completed the study.

Figure 6.a Schematic of Study Design



(a) Recommended starting dosage is 10 mg/day as ideal dosage. Dosage may be decreased to 5 mg/day at discretion of the investigator or designee.
(b) If all screening activities are completed and the subject meets the eligibility criteria the Screening and Baseline Visits can be combined into 1 visit.
(c) Subjects currently on an antidepressant at Screening will be discontinued in a manner that is consistent with labeling recommendations and conventional medical practice prior to Baseline.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

Clinical practice guidelines for the treatment of MDD suggest changing the antidepressant after unsuccessful treatment with the initial antidepressant. An open-label, single-arm, multicenter, prospective, phase 4, interventional, flexible-dose study was chosen because this type of study design is designed to better understand if vortioxetine is effective in achieving outcomes that matter to subjects, improves quality of life, and is an effective strategy to treat MDD when current antidepressant is not adequate. The single-arm design allows each subject to serve as their own "control" in comparing baseline assessments with those performed at Week 12.

6.2.2 Dose

In the current study, dosing (both initial and adjustments) will be determined by the treating physician as per routine clinical practice. The recommended starting dose is 10 mg administered orally once daily without regard to meals as per the Trintellix US Package Insert. Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in studies conducted in the United States. The effectiveness and safety of doses above 20 mg/day have not been evaluated in controlled clinical studies. A dose decrease down to 5 mg/day may be considered for subjects who do not tolerate higher doses. The dose can be reduced/increased/interrupted due to a particular AE.

6.2.3 Endpoints

The GAS, adapted for MDD, is being used in this study. As this is an adaptation of an existing instrument, the results will provide novel outcome data for the goal attainment literature. Therefore, secondary endpoint assessments with validated instruments will provide additional confirmation of the effectiveness of vortioxetine in treating MDD when current antidepressant treatment is not adequate.

The following outcome measures will be used for secondary and exploratory endpoints as they are frequently used to assess clinical response: PHQ-9, PDQ-D, Q-LES-Q, WHO-5, CGI-S, CGI-I, and [redacted].

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 (C-SSRS) 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.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 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 effectiveness of vortioxetine that indicates a change in the known risk/benefit profile for the product, such that the risk 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.
- Study meets predefined rule for futility.

6.3.2 Criteria for Premature Termination or Suspension of Study 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 Study 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 a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study 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.

7.1 Inclusion Criteria

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

1. Subject is a man or woman, aged 18 to 65 years, inclusive, and able to read and understand English.
2. Subject suffers from MDD as the primary psychiatric diagnosis.
3. Subject has been or is currently being treated with an approved antidepressant (monotherapy) for 6 weeks or longer at an adequate therapeutic dose. Subjects currently on an antidepressant at Screening will be discontinued in a manner that is consistent with labeling recommendations and conventional medical practice.
4. The subject's antidepressant treatment must be on-going at time of Screening, or have been discontinued within the 6 weeks prior to Screening.
5. Subject is considered appropriate for a change in antidepressant medication based on investigator judgment in collaboration with the subject.
6. Subject has scores on PHQ-9 ≥5 and CGI-S ≥4.
7. A female subject of childbearing potential who is sexually active 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 of study drug.
8. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
9. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.

*Definitions and acceptable methods of contraception and Contraception and Pregnancy Avoidance Procedure are defined in Section 9.1.9.Pregnancy reporting responsibilities are defined in Section 9.1.10.

7.2 Exclusion Criteria

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

1. Subject has any current psychiatric disorder other than MDD (except nonprimary concurrent anxiety), other illness or condition which may compromise the study in the opinion of the investigator.
2. Subject has discontinued prior antidepressant treatment greater than 6 weeks from Screening.

3. Subject is considered to be at imminent risk for hospitalization due to severe depression in the opinion of the investigator. Recent hospitalization due to MDD within 3 months prior to Screening is exclusionary also.
4. The subject has a significant risk of suicide according to the investigator's clinical judgment or has made an actual suicide attempt in the previous 6 months prior to Screening or scores "yes" on items 4 or 5 in the past 6 months on the Suicidal Ideation section of the C-SSRS.
5. The subject is considered to be treatment resistant, defined as patients with MDD who have not responded to 2 or more separate different antidepressant monotherapy trials of adequate dose and duration (6 weeks or longer) in their current episode. History of only responding to combination or augmentation therapy in previous MDEs is also considered evidence of treatment resistant depression.
6. The subject has received any investigational compound within 30 days prior to Screening or 5 half-lives prior to Screening, whichever is longer.
7. The subject has previously or is currently participating in this study or another vortioxetine or LuAA21004 study.
8. The subject has participated in 2 or more interventional clinical studies in the year prior to Screening, or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol.
9. 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).
10. The subject has 1 or more of the following:
    a) 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, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as determined by the investigator.
    b) Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine). The subjects must have a negative urine drug screen (UDS) at Screening and Baseline, this includes benzodiazepines and opiates (including oxycodone) for which there is no prescription (see Table 9.a).
    c) Presence or history of a clinically significant neurological disorder (including epilepsy) as determined by the investigator.
    d) Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc).

11. The subject has received vortioxetine previously, or the subject has a history of hypersensitivity or allergies to vortioxetine or any of its components.
12. Subjects receiving or who have started receiving formal cognitive or behavioral therapy, systematic psychotherapy within 30 days from Screening or plan to initiate such therapy during the study (marital therapy, and bereavement counseling are allowed).
13. The subject is receiving excluded medications (see Section 7.3) or it is anticipated that the subject will require treatment with 1 or more of the disallowed concomitant medications during the study.
14. The subject has a clinically significant unstable illness as determined by the investigator.
15. The subject has a known history of acute narrow-angle glaucoma or is at risk of acute narrow-angle glaucoma.
16. The subject has a known unstable thyroid disorder or a thyroid-stimulating hormone value outside the normal range based on medical history that is deemed clinically significant by the investigator.
17. The subject has clinically significant abnormal vital signs as determined by the investigator.
18. The subject has active hepatitis B or a known history of hepatitis C virus.
19. The subject has a known history of human immunodeficiency virus infection.
20. The subject has a history of gastric bypass.
21. The subject has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or effectiveness.
22. 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.

7.3 Excluded Medications

A list of excluded medications and treatments is provided in Table 7.a. Use of any investigational medications will be prohibited within 4 weeks 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 Excluded Medications and Treatments

Drug Class		Disallowed (X) During the Study [sections without (X) indicate no restriction]		
		Chronic Use	**Episodic Use**	**Comments or Exceptions**
Any investigational drug		X	X	
Analgesics	Narcotic analgesics	X	X	Episodic use of opiates is allowed provided the subject has a valid prescription.
	NSAIDs	X		Chronic use disallowed during the study
Antiarrhythmics (Class Ia, III, and Ic (including flecainide and propafenone)				Quinidine NOT allowed
Antibiotics				Rifampin NOT allowed
Antithrombotic agents (including low dose aspirin) and anticoagulants		X	X	
Anticonvulsants		X	X	Anticonvulsants not allowed within 6 weeks prior to Screening.
Antidepressants		X	X	Lifetime use of MAOIs and RIMAs is excluded
Antimigraine agents – triptans, dopamine antagonists		X		
Antinauseants, antiemetics (including dopamine antagonists)		X		Only phosphoric acid and bismuth preparations are allowed
Antineoplastics		X	X	
Antiobesity agents		X	X	Antiobesity agents excluded within 24 weeks prior to Screening.
Antipsychotics		X	X	Low dose allowed for sleep
Anxiolytics (including benzodiazepines)		X		Episodic use is allowed in the context of the current MDE as long the primary diagnosis continues to be MDD and not an anxiety disorder.
Cough/cold agents		X		This includes among others: dextromethorphan, phenylephrine, pseudoephedrine, low dose doxylamine contained in cough & cold agents Dextromethorphan frequent intermittent use should be monitored carefully
Herbal remedies, which are psychoactive (eg, St. Johns Wort, kava kava, valerian, ginkgo biloba, melatonin)		X	X	
Mood stabilizers		X	X	Lifetime use is excluded
Muscle relaxants, centrally acting agents		X	X	
Sedatives/hypnotics		X		Episodic use is allowed in the context of the current MDE.
Psychotropic agents not otherwise specified (including psychostimulants, tryptophan, melatonin and dopamine agonists)		X	X	Not allowed within 6 weeks prior to Screening.

MAOI=monoamine oxidase inhibitor, NSAID=nonsteroidal anti-inflammatory drug, RIMA=reversible inhibitor of monoamine oxidase A.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.12.

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 drug 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), if the following circumstances occur at any time during study drug treatment:

     – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8× upper limit of normal (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 drug 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. 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 in the subject's source documents.
4. 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. The specific reasons for discontinuation from study drug will be collected for both the subject and as determined by the investigator.

   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 should not be recorded in the "voluntary withdrawal" category). Similarly, lack of effectiveness should not be recorded in the "voluntary withdrawal" category.
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

6. 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 9.1.10.

7. Lack of effectiveness. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.

7.5 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 7.4. 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 Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications 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 study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

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

- Commercial vortioxetine tablets in strengths of 5, 10, and 20 mg.

Vortioxetine 5, 10, and 20 mg tablets are manufactured by Takeda or H. Lundbeck A/S, Valby, Denmark.

8.1.1.1 Study drug

Vortioxetine is a compound developed by Takeda and H. Lundbeck A/S as an antidepressant and treatment for MDD. Vortioxetine was approved in September 2013 and commercialized in the United States in January 2014. Vortioxetine belongs to a new chemical class of psychotropics, the bis-arylsulfonyl amines, which possess unique properties compared with currently known psychotropics. This class of compounds is structurally different from all currently known psychotropics.

Vortioxetine is commercially formulated as immediate-release tablets intended for oral administration.

The study drug will be packaged in high-density polyethylene bottle with child resistant closures. Each bottle contains 28 daily doses plus 7 extra tablets for a total of 35 tablets per bottle to be dispensed at the visits indicated in the Schedule of the Study Procedures (Appendix A). The subjects will be required to take 1 tablet orally, at the same time of day, preferably in the morning, or as directed. The study drug will be labeled with a single label and dispensed as open-label for the 12-week treatment phase. The study drug will be identifiable by a unique identification (ID) number that will be assigned by an IxRT. Each bottle will be labeled with pertinent study information.

8.1.1.2 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following: Commercial vortioxetine tablets in strengths of 5, 10, and 20 mg.

8.1.2 Storage

Study medication should be stored at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Vortioxetine 5, 10, and 20 mg must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Vortioxetine 5, 10, and 20 mg 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 dosing (both initial and adjustments) will be determined by the investigator or designee as per routine clinical practice and per approved labeling.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the treating physician per routine standard of care.

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. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

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

In the event of deliberate or accidental 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 measures 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 drug overdose.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to begin the study drug with the recommended starting dose of 10 mg/day administered orally once daily without regard to meals. Based on the discretion of the investigator or designee, dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States. A dose decrease down to 5 mg/day may be considered for subjects who do not tolerate higher doses. The investigator (or designee) may increase or decrease the dosage at any time. Dose adjustments should occur during regularly scheduled visits, or subjects should return for an unscheduled visit.

The investigator or the investigator's designee will access the IxRT at Screening to obtain the subject study number. The investigator or the investigator's designee will utilize the IxRT to enroll the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening.

The medication ID number of the sponsor-supplied drug to be dispensed will then be provided by the IxRT. If sponsor-supplied drug (vortioxetine) is lost or damaged, the site can request a replacement from IxRT (refer to IxRT manual provided separately). At subsequent drug-dispensing visits, the investigator or designee will again access IxRT to request additional sponsor-supplied drug for a subject. The medication ID number of the study drug to be dispensed will be provided by the IxRT.

8.3 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 QD), 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 IxRT. 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/job 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 IxRT 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 drug (vortioxetine) on a sponsor-approved drug accountability log. 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, expiry and/or retest date, date and amount

dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature 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.

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.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites. The on-site pharmacist (site designee) will immediately return unused study drugs to the sponsor.

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/that informed consent is explained. This subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

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

9.1.2 Demographics, Medical History, Medication History, and Disease History Procedure

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

Medical and psychiatric history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent, specifically psychiatric and MDD history as well as previous treatments related to psychiatric and MDD history. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.6). Additionally, the factors for determining a change/discontinuation from the prior antidepressant as assessed by the subject and by the investigator will be collected.

Medication history information to be obtained includes any medication relevant to eligibility criteria and effectiveness/safety evaluation stopped at or within 12 weeks prior to signing of informed consent.

9.1.3 Weight and Height

A subject should have weight measured while wearing indoor clothing and with shoes off during Screening, Baseline, and Week 12. Height, measured at Screening only, is recorded in centimeters without decimal places. Weight is collected in kilograms with 1 decimal place.

9.1.4 Vital Sign Procedure

Vital signs will include blood pressure, pulse, and temperature will be performed during the Screening Visit.

9.1.5 Documentation of Concomitant Medications

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

9.1.6 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the time of signing the informed consent. This includes clinically significant laboratory or physical examination abnormalities noted at Screening/Baseline examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.7 Effectiveness Patient Reported Outcomes and Health Economic Outcome Research (HEOR) Assessments

The following assessments will be conducted during the Treatment Period of the study, unless otherwise indicated.

9.1.7.1 GAS

The GAS [17,18] is a tool to measure the progress each subject has towards achieving their individualized goals. While the outcome measure is unique to each subject, standardized scoring is applied to allow for statistical analysis.

The GAS allows for 1 of 2 types of goals to be set:

1. Subject defined goals, allow a “subject’s chief complaint” approach taken towards establishing the goal, with no specific limitations set for the type or focus of the goal, beyond requiring that it meets the basic standards of measurability, equidistance, and difficulty.
2. Domain-Defined goals are more structured in nature, presenting the subject with an array of broadly defined domains and more specific subdomains. After selecting an appropriate domain and (where applicable) subdomain, the clinician will work with the subject to establish a specific goal that fits within the selected category.

For GAS, a total of 3 goals will be selected, 1 subject defined and 2 from pre-defined domain categories. A 5-point rating scale will then be applied to each of the 3 goals. A semistructured interview will be conducted with each subject to conduct goal-setting at the outset of the study.

Another evaluation will take place at Week 6 and Week 12/End of Study visits or at Early Termination Visit (as applicable) to determine the level of progress at that time, with assignment of appropriate scores. It takes subjects approximately 45 minutes to complete the GAS.

9.1.7.2 PHQ-9

The PHQ-9 [19] will be used as a secondary efficacy measure of depression severity. This is a well-established patient reported outcome tool for assessment of change in depressive symptoms and is a sensitive measure of depression severity.

The PHQ-9 consists of a 9-item scale originally developed for primary care settings, with 1 item corresponding to each of the 9 MDE symptom criteria for depression in DSM, asking if they have bothered the patient over the last 2 weeks. Each question is rated on a scale from 0 (not at all) to 3 (nearly every day). If any problems are answered 1 or higher, a final question on how difficult those problems made it to do work, take care of things at home, or get along with other people is completed, rated from not difficult at all to extremely difficult. The 9 questions are summed to a total score ranging from 0 to 27 with higher scores reflecting greater severity. It takes approximately 5 minutes to complete the PHQ-9.

9.1.7.3 PDQ-D

The PDQ-D [20], a validated version of the original PDQ specifically modified to depressed patients, will be used to evaluate self-reported cognitive complaints in patients with MDD. The PDQ was originally developed to assess cognitive complaints in patients with multiple sclerosis. However, it does address cognitive aspects highly relevant for depression, including attention and concentration, retrospective memory, prospective memory, and planning and organization. It takes approximately 10 minutes to complete the PDQ-D.

9.1.7.4 Clinical Global Impression Scales

The CGI was developed to provide global measures of the severity of a patients clinical condition during clinical studies. The CGI scales consist of 2 subscales: the CGI-S and the CGI-I [21]. CGI-S and CGI-I raters will be required to have suitable experience and training (as deemed by sponsor) to be eligible to rate subjects within the study. The total time to score the CGI is approximately 1 to 2 minutes after the clinical interview.

CGI-S

The CGI-S is a clinician rated scale designed to assess global severity of illness and change in the clinical condition over time. The CGI-S provides the clinician's impression of the patient's current state of mental illness. The clinician uses his or her clinical experience of this patient population to rate the severity of the patient's current mental illness on a 7-point scale ranging from 1 (normal - not at all ill) to 7 (among the most extremely ill patients).

CGI-I

The CGI-I assesses the subject's improvement (or worsening). The clinician is required to assess the subject's condition relative to Baseline (Randomization/Day 1) 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.

9.1.7.5 Company

Company Confidential Information

[redacted]

9.1.7.6 Company Confidential

Company Confidential Information

[redacted]

9.1.7.7 C-SSRS

The C-SSRS [25] Baseline/Screening will be administered at Screening and the Since-Last-Visit C-SSRS will be administered at all other time points. The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial of centrally acting drugs. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing severity. The tool is administered via an interview with the subject. If possible, the same interviewer should be used throughout the study for the same subject. It takes approximately 10 minutes to complete the C-SSRS.

9.1.7.8 Q-LES-Q

The Q-LES-Q [26] is a scale designed to allow researchers to assess the degree of a subject's quality of life in various areas of daily living. Ninety-one of the 93 items are assembled into

8 categories: physical health/activities, feelings, work, household duties, school/course work, leisure time activities, social relations, and general activities. Items are scored on a 5-point scale, from 1 (not at all or never) to 5 (frequently or all the time), to indicate the degree of enjoyment or satisfaction experienced. Higher scores indicate greater enjoyment/satisfaction. Typically a self-report measure, this scale will be read to the subject by a member of the site staff and verbatim answers recorded to ensure all data points are captured. It takes approximately 40 to 45 minutes to complete the Q-LES-Q.

9.1.7.9 WHO-5

The WHO-5 [27,28] is a short, self-administered questionnaire covering 5 positively worded items, related to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interests (being interested in things). Administering the WHO-5 takes 2 to 3 minutes to complete.

9.1.7.10 Company Confident

Company Confidential Information

[redacted]

9.1.7.11 Company Confidenti

Company Confidential Information

[redacted]

9.1.7.12 Order of Assessments

The order of assessments is not defined, it is recommended that the WHO-5 and the CGI-I/CGI-S, as applicable, are done after the completion of all other assessments.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 19 mL, and the approximate total volume of blood for the study is 46 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Limited Serum Chemistry
RBC	ALT
WBC	Albumin
Hemoglobin	Alkaline phosphatase
Hematocrit	AST
Platelets	Total bilirubin
Neutrophils	Direct bilirubin
Eosinophils	
Basophils	
Lymphocytes	
Monocytes	

Other:

Serum	Urine
Female subjects : hCG (a,c)	Female subjects only: hCG (b) All subjects: Urine drug and alcohol screen including: amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone and phencyclidine (d)

hCG=human chorionic gonadotropin, RBC=red blood cell, WBC=white blood cell.
(a) Urine hCG pregnancy tests will be performed at Screening and for all other visits during the Treatment Period for women of childbearing potential only.
(b) Urine hCG must be negative at Visit 2 prior to enrollment. 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 1 year since last regular menses with a follicle-stimulating hormone [FSH]>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).
(c) Serum hCG pregnancy tests will be performed at Baseline and End of Study/Early Termination visits on all females. For combined Screening and Baseline Visits, there will be 1 urine and 1 serum hCG. Subjects (women of childbearing potential) may be enrolled with a negative urine hCG; however if the serum hCG is positive the subject must be withdrawn from study drug immediately and withdrawn from the study as soon as possible.
(d) The subject must have a negative UDS. This includes benzodiazepines and opiates for which there is no prescription (including oxycodone) at Screening and Baseline performed locally by the site.

Urine drug screen test kits will be supplied by the sponsor for UDS testing at the clinic. Urine for drug screening will not be sent to the central laboratory for testing. The central laboratory will perform laboratory tests for serum pregnancy, hematology and limited serum chemistries. Local UDS and urine pregnancy screening results must be confirmed prior to conducting the Baseline Visit. Serum pregnancy collected at Baseline should be sent to the central laboratory. In the case of a combined Screening and Baseline Visit the UDS and the urine pregnancy test will be done once in the clinic and a serum pregnancy test will be sent to the central laboratory. The results of central laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to72 hours after the abnormality

was noted. (Refer to Section 7.4 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

If 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 sponsor-supplied drug. discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3).

9.1.9 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 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 1 year since last regular menses with a FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

9.1.9.1 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH>40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly)". In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
   - Nonhormonal methods:
     - IUD.
     - Bilateral tubal occlusion.

  - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
  - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose, throughout the duration of the study, and for 30 days after completion of the study.

- Hormonal Methods. (Vortioxetine has been shown not to interact with hormonal contraceptives.)
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months:
    - Oral.
    - Intravaginal (eg, ring).
    - Transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months:
    - Oral.
    - Injectable.
    - Implantable.

2. Effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.

- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.

4. Subjects will be provided with information on highly effective/effective 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, donation of ova donation during the course of the study.
5. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential. Women of childbearing potential will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Reasons for use of barrier methods (ie, condom).
   c) Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late? (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes").
      iv. Is there a chance you could be pregnant?
6. In addition to a negative urine hCG pregnancy test at Screening, Female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine hCG pregnancy test prior to receiving any dose of study medication (as close as possible and prior to first dose of study medication, preferably on the same day).

9.1.10 Pregnancy

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

If the pregnancy occurs during administration of active study medication, eg, after Visit 2 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 1.1.

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.

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.

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 PGx Sample Collection

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

Two 3-mL whole blood samples for DNA isolation will be collected at the Baseline Visit before dosing from each subject in the study, into plastic K_2EDTA spray-coated tubes, and stored under frozen conditions.

Two whole blood samples (2.5 mL per sample) for RNA isolation will be collected at the Baseline Visit before dosing and at the Week 12/Early Termination (Visit 6) into PAXgene tubes, and stored under frozen conditions.

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.

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.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at screening, the investigator should complete the eCRF. The IxRT 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 identification numbers assigned to subjects who fail screening should not be reused.

9.1.13 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.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers/unused study medication to each dispensing site visit. All supplies used to administer study drug to the subject will be recorded on the eCRFs.

If a subject is persistently noncompliant with study drug (eg, less than 70% compliant or greater than 125% 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 discussion 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 -1)

Subjects will may be screened within 21 days prior to Baseline. Procedures to be completed during the Screening Visit are detailed in Appendix A. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.12 for

procedures for documenting screening failures. IxRT will be accessed for the subject screening number. The factors for determining a change/discontinuation from the prior antidepressant as assessed by the subject and by the investigator will be collected. The Screening and Baseline Visits may be combined if determined appropriate per the investigator. Any procedure that is to be performed at both visits should only be conducted once for a combined visit.

9.3.2 Study Entrance/Baseline Visit 2 (Day 1)

Study enrollment will take place on Day 1 (Baseline, Visit 2). Procedures to be completed during the Baseline Visit are detailed in Appendix A.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for enrollment, the subject should be enrolled and study drug should be dispensed using the IxRT, as described in Section 8.2. Subjects will be instructed on when to take the first dose of study drug. The procedure for documenting Screening failures is provided in Section 9.1.12. The factors for determining a change/discontinuation from the prior antidepressant as assessed by the subject and by the investigator will be collected.

9.3.3 Open-Label Treatment Visits 3 and 5: Week 2 (Day 15), and Week 6 (Day 43)

The Subjects will return to the study site for their Week 2 (Visit 3) and Week 6 (Visit 5) Visits. Subjects will be instructed to return their bottle of study drug dispensed at the previous visit for drug accountability. Procedures to be completed during Visits 3 and 5 are detailed in Appendix A.

9.3.4 Telephone Visit 4 and 6: Week 4 (Day 29) and Week 9 (Day 64)

A telephone visit will occur at Visit 4 (Week 4) and 6 (Week 9). Procedures to be completed during Visits 4 and 6 are detailed in Appendix A.

9.3.5 Final Visit or Early Termination

The Final Visit will be performed at Visit 7 (Week 12) or at Early Termination Visit. For all subjects receiving study drug, the investigator must complete the End of Study eCRF page. Procedures to be completed during Final Visit/Early Termination Visit are detailed in Appendix A.

For subjects who permanently discontinue study drug early, all Final Visit/Early Termination assessments detailed in Appendix A should be performed in close proximity to, or at the time of, study drug discontinuation.

At the End of Study Visit the Clinician and subject satisfaction with the antidepressant treatment will be collected. In addition, Clinician and subject satisfaction with the GAS approach as a method for establishing treatment goals, evaluating progress towards treatment goals, and improving communication between clinicians and patients will be collected.

9.3.6 Unscheduled Visit

Unscheduled visits may occur at any time after the Week 2 visit.

Subjects may return to the study center for unscheduled visits as needed. Unscheduled study visits can be performed when the subject has a study related issue in between regular study visits. The following procedures should be performed during this visit:

- Concomitant medications.
- AE assessment.
- Other procedures, including dose adjustments, as deemed appropriate by the investigator.

9.3.7 Safety Follow-up Phone Call (Week 16 or Early Termination)

A safety follow-up phone call will be made 28 days (±7 days) after withdrawal from the study or after completion of the study. A concomitant medication and AE assessment will be completed.

9.3.8 Poststudy Care

Sponsor-supplied drug 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 PGx Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.11. The genetic material will be preserved, retained, and initially stored at PPD Central Laboratory and then preserved and retained for long-term storage at Covance Central Laboratory 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 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 PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time. Sponsor must be notified of the 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 drug; 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 value), 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 or 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 drug 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 eCRF page.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or electrocardiogram [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 findings 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 or ECG re-test and/or continued monitoring of an abnormal value or finding 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) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious, or severe in nature. 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 medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. 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 the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, 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 intensity of AEs /Serious PTEs:

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

Preplanned procedures (surgeries or interventions):

- 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 recorded 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 effectiveness):

- Insufficient clinical response, effectiveness, 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 effectiveness.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

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

1. Results in DEATH.
2. 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.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. 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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

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 AEs of Special Interest

AEs of special interest are to be reported and followed up in the same manner of other AEs (see Section 10.2.2).

An AE of Special Interest (serious or nonserious) 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. The reporting of specific AE of Special Interest are described in the following sections.

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 7.4 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 drug, discussion of the relevant subject details and possible alternative causalities.

If a subject is noted to have an ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.3.1. In addition, an LFT increases eCRF must be completed and transmitted with the SAE.

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 Intensity 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 drug(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 medications 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 medications 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 investigator.

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 Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular 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 1 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 drug (Baseline Visit 1) or until screen failure. For subjects who discontinue prior to study drug 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 drug (Baseline Visit 1). Routine collection of AEs will continue for 4 weeks 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.

Nonserious 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 drug 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. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

All outcomes used in this study will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 AEs of Special Interest

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.

If the AE of special interest/abnormality, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in an AE Form or an SAE Form. The Form should be completed and reported to the clinical contract research organization (CRO)/Pharmacovigilance department within 24 hours.

Special interest AE/abnormality criteria include:

- Laboratory value threshold, if applicable.
- Premature termination for the AE of Special Interest, if applicable.
- Any other specific criteria.

AEs of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

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 drug(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.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory

tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (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 or IECs, 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, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries 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 report 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 a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC.

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 medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

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

The sponsor or its designee will supply study 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. 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 e-sign 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 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, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. 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 Council for Harmonisation (ICH) E6(R2) Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) 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 study site agreement between the investigator and sponsor.

Refer to the 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 will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to 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

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS), and safety analysis set. The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The FAS, used for primary effectiveness analysis, will include all subjects who were enrolled in the treatment period and received at least 1 dose of the study drug and completed at least 1 GAS assessment post-Baseline. In FAS effectiveness summaries, subjects will be considered as vortioxetine treated no matter what dose levels were received during the study.

A 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 prescribed by the treating physician, will be identified in the minutes of the subject evaluability assessment.

The Safety Set will include all subjects who were enrolled and received at least 1 dose of study medication. In safety summaries, all subjects will be analyzed as vortioxetine-treated.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, with consulting a medical expert as needed. If necessary, the Handling Rules for Analysis Data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using mean, SD, median, maximum, and minimum values. Study drug information, including dose, frequency, and duration will be summarized. An end of study form/study disposition summary will also be provided.

13.1.3 Effectiveness Analysis

The primary objective of the study is to determine the effectiveness of treatment with vortioxetine on subject goal achievement after changing antidepressant medication for treatment of MDD. The

primary endpoint is the proportion of subjects who changed to treatment with vortioxetine who achieve their individually identified goals as demonstrated by an outcome GAS Score of ≥50 at Week 12. This proportion will be summarized at Week 12.

For the secondary endpoints of outcome measures of GAS Score, PHQ-9, PDQ-D, Q-LES-Q Score, WHO-5, and CGI-S, total scores and changes from Baseline will be summarized by each time point of Baseline, Week 6 (as appropriate) and by each time point of Baseline and Week 12. These changes from Baseline will be analyzed using paired t-tests. Also, for each of the outcome measurements, change from Baseline at Week 12 will be analyzed using paired t-tests. Tests of significance will be 2-tailed with alpha level at 0.05. CGI-I Scores will be summarized at Week 12 using descriptive statistics.

[redacted]

Additional analysis will be performed for other additional endpoints, if necessary.

13.1.4 Safety Analysis

AEs will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis will be performed once 60 subjects complete the study. A futility assessment will be done at this time. If the futility criteria is met, the study may be stopped. The end of the study will be the date of the last safety follow-up visit of the last subject completed.

13.3 Determination of Sample Size

As no formal hypothesis testing is performed for the primary endpoint, the purpose of sample size estimation is to determine the adequate sample size needed to provide a precise estimate for the response rate (GAS Score ≥50) with 95% CIs.

Conservatively estimating that 50% of subjects will be responders (GAS≥50) and that 100 subjects will complete the study, CIs will be ±0.098 around the point estimate (proportion of responders).

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 guarantees 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 sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, 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.

The investigator should document all protocol deviations.

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 Food and Drug Administration, 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 guarantees 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. 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 study. Until the site receives drug/notification no protocol activities, including screening may occur.

Study 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 trial database or documentation via a subject 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 the monitor or the sponsor's designee, representatives from any regulatory authority (eg, Food and Drug Administration, 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 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 as recommended by the International Committee of Medical Journal Editors (www.icmje.org). All publications and presentations must be prepared in accordance with this section and the study site agreement and Good Publication Practice guidelines, Battisti et al

[31]. In the event of any discrepancy between the protocol and the study site agreement, the 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 all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/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 study 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 the sponsor providing this information to callers must provide the sponsor 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 and/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 study subjects. Refer to the 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.

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Appendix A Schedule of Study Procedures

	Screening	Treatment						Telephone Follow-up
	Visit 1 (a)	Baseline Visit 2 (a) Day 1	Visit 3 Wk 2	Telephone Contact Visit 4 Wk 4	Visit 5 Wk 6	Telephone Contact Visit 6 Wk 9	End of Study Visit 7 Wk 12 /Early Termination	Visit 8 Wk 16
	Days -21 up to -1	Day 1	Day 15 (±3 Days)	Day 29 (±3 Days)	Day 43 (±5 Days)	Day 64 (±5 Days)	Day 85 (±5 Days)	Day 113 (± 7 Days)
Informed consent	X							
Eligibility criteria	X	X						
Demographics, medical history, medication history	X							
UDS (b)	X	X						
MDD diagnosis confirmed by investigator judgment, antidepressant medication history & disease history	X							
Height and weight (c)	X	X					X	
Hematology and limited serum chemistry		X					X	
PGx sample collection (d)		X					X	
Concurrent medical conditions	X	X						
Concomitant medications		X	X	X	X	X	X	X
Vital signs	X							
GAS assessment		X			X		X	
PHQ-9	X	X			X		X	
Q-LES-Q		X					X	
PDQ-D		X			X		X	
Company Confidential Information								
Company Confidential Information								
Company Confidential Information								
C-SSRS	X	X	X		X		X	
Company Confidential Information								
WHO-5		X			X		X	
CGI-S	X	X	X		X		X	
CGI-I			X		X		X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening	Treatment						Telephone Follow-up
	Visit 1 (a)	Baseline Visit 2 (a) Day 1	Visit 3 Wk 2	Telephone Contact Visit 4 Wk 4	Visit 5 Wk 6	Telephone Contact Visit 6 Wk 9	End of Study Visit 7 Wk 12 /Early Termination	Visit 8 Wk 16
	Days -21 up to -1	Day 1	Day 15 (±3 Days)	Day 29 (±3 Days)	Day 43 (±5 Days)	Day 64 (±5 Days)	Day 85 (±5 Days)	Day 113 (± 7 Days)
Document factors for determining a change/discontinuation from prior antidepressant (e)	X							
PTE/AE assessment	X	X	X	X	X	X	X	X
Pregnancy testing and pregnancy avoidance counseling (f,g)	X	X	X		X		X	
Access IxRT for subject ID/ medication ID/subject status	X	X	X		X		X	
Dispense study drug		X	X		X			
Dose adjustment (as needed) (h)			X		X			
Clinician and subject satisfaction with change in antidepressant							X	
Clinician and subject satisfaction with GAS approach							X	
Study drug return/accountability/ compliance			X		X		X	

(a) Screening and Baseline Visits may be combined as determined appropriate per the investigator. Any procedure that is to be performed at both visits should only be conducted once for a combined visit.
(b) UDS to be done at Screening and Baseline. UDS kits will be supplied by the sponsor for the testing at the clinic. UDS results must be negative. This includes benzodiazepines and opiates for which there is no prescription (including oxycodone) at Screening and Baseline. Results must be confirmed prior to conducting the Baseline Visit.
(c) Height at Screening only; weight at Screening, Baseline, and Week 12.
(d) Subjects who signed an informed consent for PGx testing will have blood samples for PGx analysis and these will be collected as follows: 2×3 mL for DNA on Day 1; 2×2.5 mL for RNA predose on Day 1 and at Week 12 (Visit 6).
(e) To be collected at Screening or combined Screening/Baseline Visit.

(f) Urine hCG pregnancy tests will be performed at Screening and Baseline and for all other visits during the Treatment Period for women of childbearing potential only. Serum hCG pregnancy tests will be performed at Baseline and End of Study/Early Termination visits for all females. For combined Screening and Baseline Visits, there will be 1 urine and 1 serum hCG. Subjects may be enrolled with a negative urine hCG; however, if the serum hCG is positive the subject must be withdrawn from study drug immediately and withdrawn from the study as soon as possible.
(g) Subject who are women of childbearing potential 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 of pregnancy and donation of ova during the course of the study and for 30 days after the last dose of study drug.
(h) Dose adjustments should occur during regularly scheduled visits, or subjects should return for an Unscheduled Visit.

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 investigator agrees to assume the following responsibilities:

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 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 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 or the subject's legally acceptable representative 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 drug(s), studying other therapies for subjects, 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 women of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 5 half lives PLUS 30 days after last dose. Regular pregnancy tests will be performed throughout the study for all female women of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. 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 drug.
- 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 Detailed Description of Amendments to Text

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

Page 2, Section 1.1 Contacts

Existing Text

Responsible Medical Officer (carries overall responsibility for the conduct of the study)	*Steve Chen, MD* Takeda Pharmaceuticals USA US Medical *Affairs* 224-554-*3121*

Revised Text

Responsible Medical Officer (carries overall responsibility for the conduct of the study)	**Louis Mini, MD** **Medical Head, CNS** Takeda Pharmaceuticals USA US Medical **Office** 224-554-**6195**

Rationale for Amendment

Change in personnel.

Page 3, Section 1.1 Contacts

Page 5, Investigator Agreement

Page 61, Section 12.2 Record Retention

Existing Text

- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.

Revised Text

- International **Council for** Harmonisation E6**(R2)** Good Clinical Practice: Consolidated Guideline.

Rationale for Amendment

ICH name has changed and guidelines have been revised.

Page 3, Section 1.2 Approval

Existing Text

Personal Protected Data *Date*

Personal Protected Data *Date*

Personal Protected Data *Date*

Personal Protected Data *Date*

Personal Protected Data *Date*

Revised Text

Personal Protected Data

Rationale for Amendment

Change in personnel.

Page 11, Section 2.0 Study Summary, Study Design, 5th Paragraph

Page 24, Section 6.1 Study Design, 9th Paragraph

Existing Text

A futility analysis *will* be performed at an interim analysis after approximately 60 subjects have completed *Week 12*.

Revised Text

A futility analysis **may** be performed at an interim analysis after approximately 60 subjects have completed **the study**.

Rationale for Amendment

Analysis will be completed once 60 subjects have completed the safety follow up.

Page 13, Section 2.0 Study Summary, Main Criteria for Exclusion, Criterion #4

Page 28, Section 7.2 Exclusion Criteria, Criterion #4

Existing Text

The subject has a significant risk of suicide according to the investigator's clinical judgment or has made an actual suicide attempt in the previous 6 months prior to Screening or scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS.

Revised Text

The subject has a significant risk of suicide according to the investigator's clinical judgment or has made an actual suicide attempt in the previous 6 months prior to Screening or scores "yes" on items 4 or 5 in the **past 6 months on the** Suicidal Ideation section of the C-SSRS.

Rationale for Amendment

The intent of this criterion is to exclude subjects who currently have significant risk of suicide (according to the investigator's clinical judgment), or made an actual suicide attempt in the previous 6 months prior to Screening, or within the same time frame have had active suicidal ideation with some intent to act (item 4 of CSSRS) or have had active suicidal ideation with specific plan and intent to act (item 5 of CSSRS). A lifetime "yes" answer to items 4 and 5 will not exclude the subject, but a "yes" answer to past 6 months for items 4 and 5 is exclusionary.

Page 17, Section 3.3 List of Abbreviations

New and Revised Text

ICH	International **Council** for Harmonisation
STAR*D	**Sequenced Treatment Alternatives to Relieve Depression**
US	**United States**
WAIS-IV	**Wechsler Adult Intelligence Scale Fourth Edition**

Rational for Amendment

Clarification of text.

Page 20, Section 4.2 Rationale for the Proposed Study

Existing Text

Data from clinical studies regarding switching antidepressant medication rates is minimal and the rationale for the switch varies across studies [12]. Claims databases have shown switching rates for antidepressants have ranged from 2.78% to 13.7% [13,14]. The results of switching, in particular, multiple switching can lead to suboptimal outcomes for patients. Results of the STAR-D *project* showed that as the number of switches increased the burden of illness, including relapse rates, also increased. Relapse may trigger a pharmacologic switch [15]. Switching antidepressant agents has been shown to increase treatment costs and can be burdensome to the patient, so it is important to get the patient to the optimal treatment as early as possible in the therapeutic pathway [16].

Revised Text

Data from clinical studies regarding switching antidepressant medication rates is minimal and the rationale for the switch varies across studies [12]. Claims databases have shown switching rates for antidepressants have ranged from 2.78% to 13.7% [13,14]. The results of switching, in particular, multiple switching can lead to suboptimal outcomes for patients. Results of the **Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study** showed that as the number of switches increased the burden of illness, including relapse rates, also increased. Relapse may trigger a pharmacologic switch [15]. Switching antidepressant agents has been shown to increase treatment costs and can be burdensome to the patient, so it is important to get the patient to the optimal treatment as early as possible in the therapeutic pathway [16].

Rational for Amendment

Clarification of text.

Page 22, Section 5.2.3 Additional Endpoints

New Text

- Summary of level of satisfaction with study treatment and the goal attainment approach among clinicians and subjects.

Rational for Amendment

Documentation of antidepressant change, and satisfaction with change in treatment was noted in Section 9.3, but was not listed in the table of procedures in error. Clinician and subjects satisfaction with GAS is being added to assess the GAS approach in clinical practice and to guide future GAS work.

Page 40, Section 9.1.7.5 Company Confidential

Existing Text

Company Confidential Information [redacted]

Revised Text

Company Confidential Information [redacted]

Rationale for Amendment

Company Confidential Information [redacted]

Page 43, Section 9.1.9 Contraception and Pregnancy Avoidance Procedure

Existing Text

From signing of informed consent, throughout the duration of the study, and for *4 weeks* after last dose of study medication, female subjects of childbearing potential must use adequate contraception. In addition, they must be advised not to donate ova during this period.

Revised Text

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 must use adequate contraception. In addition, they must be advised not to donate ova during this period.

Rationale for Amendment

To keep language consistent with inclusion criteria**.**

Page 44, Section 9.1.9.1 Definitions and Procedures for Contraception and Pregnancy Avoidance, Nonhormonal Methods

Existing Text

- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose, throughout the duration of the study, and for *4 weeks* after completion of the study.

Revised Text

- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose, throughout the duration of the study, and for **30 days** after completion of the study.

Rationale for Amendment

To keep language consistent with inclusion criteria.

Page 45, Section 9.1.10 Pregnancy, 2nd Paragraph

Existing Text

If the pregnancy occurs during administration of active study medication, eg, after Visit 2 or within *4 weeks* 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 1.1.

Revised Text

If the pregnancy occurs during administration of active study medication, eg, after Visit 2 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 1.1.

Rationale for Amendment

To keep language consistent with inclusion criteria**.**

Page 46, Section 9.1.11 PGx Sample Collection, 3rd Paragraph

Existing Text

Two whole blood samples (2.5 mL per sample) for RNA isolation will be collected at the Baseline Visit before dosing and at the Week 12/Early Termination (Visit 6) into *plastic K_2EDTA spray-coated* tubes, and stored under frozen conditions.

Revised Text

Two whole blood samples (2.5 mL per sample) for RNA isolation will be collected at the Baseline Visit before dosing and at the Week 12/Early Termination (Visit 6) into **PAXgene** tubes, and stored under frozen conditions.

Rationale for Amendment

Incorrect collection tube was listed.

Page 47, Section 9.3.1 Screening Visit 1 (Days -21 to -1)

Existing Text

Subjects will may be screened within 21 days prior to Baseline. Procedures to be completed during the Screening Visit are detailed in Appendix A. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.12 for

procedures for documenting screening failures. IxRT will be accessed for the subject screening number. The Screening and Baseline Visits may be combined if determined appropriate per the investigator. Any procedure that is to be performed at both visits should only be conducted once for a combined visit.

Revised Text

Subjects will may be screened within 21 days prior to Baseline. Procedures to be completed during the Screening Visit are detailed in Appendix A. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.12 for procedures for documenting screening failures. IxRT will be accessed for the subject screening number. **The factors for determining a change/discontinuation from the prior antidepressant as assessed by the subject and by the investigator will be collected.** The Screening and Baseline Visits may be combined if determined appropriate per the investigator. Any procedure that is to be performed at both visits should only be conducted once for a combined visit.

Rational for Amendment

This was noted at Baseline only, but should collected at Screening or combined Screening/Baseline Visit.

Page 48, Section 9.3.5 Final Visit or Early Termination

Existing Text

The Final Visit will be performed at Visit 7 (Week 12) or at Early Termination Visit. For all subjects receiving study drug, the investigator must complete the End of Study eCRF page. Procedures to be completed during Final Visit/Early Termination Visit are detailed in Appendix A.

For subjects who permanently discontinue study drug early, all Final Visit/Early Termination assessments detailed in Appendix A should be performed in close proximity to, or at the time of, study drug discontinuation.

*The factors for determining a change/discontinuation from the prior antidepressant as assessed by the subject and by the investigator will be collected at the Final Visit and Early Termination (as applicable). Additionally a*t the End of Study Visit the Clinician satisfaction with the *change in* antidepressant will be collected.

Revised Text

The Final Visit will be performed at Visit 7 (Week 12) or at Early Termination Visit. For all subjects receiving study drug, the investigator must complete the End of Study eCRF page. Procedures to be completed during Final Visit/Early Termination Visit are detailed in Appendix A.

For subjects who permanently discontinue study drug early, all Final Visit/Early Termination assessments detailed in Appendix A should be performed in close proximity to, or at the time of, study drug discontinuation.

At the End of Study Visit the Clinician **and subject** satisfaction with the antidepressant **treatment** will be collected. **In addition, Clinician and subject satisfaction with the GAS approach as a**

method for establishing treatment goals, evaluating progress towards treatment goals, and improving communication between clinicians and patients will be collected.

Rational for Amendment

Documentation of antidepressant change, and satisfaction with change in treatment was noted in Section 9.3, but was not listed in the table of procedures in error. Clinician and subjects satisfaction with GAS is being added to assess the GAS approach in clinical practice and to guide future GAS work.

Page 52, Section 10.1.4 SAEs, Criterion #5

Existing Text

Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

Revised Text

Is a CONGENITAL ANOMALY/BIRTH DEFECT.

Rationale for Amendment

Error in original text.

Page 64, Section 13.1.3 Effectiveness Analysis

New Text

Additional analysis will be performed for other additional endpoints, if necessary.

Rationale for Amendment

To allow for analysis of additional endpoints.

Page 64, Section 13.2 Interim Analysis and Criteria for Early Termination

Existing Text

No further subjects will be enrolled once approximately 60 subjects have completed their Week 12 visit. At this point, an interim futility analysis will be performed. If the futility criteria is met, the study *will* be stopped*. Otherwise, an additional 60 subjects will be enrolled.* The end of the study will be the date of the last safety follow-up visit of the last subject *based either on the first 60 completed subjects or the final 120 completed subjects.*

Revised Text

An interim analysis will be performed **once 60 subjects complete the study**. **A futility assessment will be done at this time.** If the futility criteria is met, the study **may** be stopped. The end of the study will be the date of the last safety follow-up visit of the last subject **completed.**

Rationale for Amendment

Analysis will be completed once 60 subjects have completed, but enrollment will not be stopped.

Page 74, Appendix A Schedule of Study Procedures Telephone Follow-up Window

Existing Text

Telephone Follow-up
Visit 8 Wk 16
Day 113 (± *3* Days)

Revised Text

Telephone Follow-up
Visit 8 Wk 16
Day 113 (± **7** Days)

Rationale for Amendment

Clarification of text to match the body of the protocol.

Page 75, Appendix A Schedule of Study Procedures

Existing Text

	Screening	**Treatment**						**Telephone Follow-up**
	Visit 1 (a)	**Baseline Visit 2 (a) Day 1**	**Visit 3 Wk 2**	**Telephone Contact Visit 4 Wk 4**	**Visit 5 Wk 6**	**Telephone Contact Visit 6 Wk 9**	**End of Study Visit 7 Wk 12 /Early Termination**	**Visit 8 Wk 16**
	Days -21 up to -1	**Day 1**	**Day 15 (±3 Days)**	**Day 29 (±3 Days)**	**Day 43 (±5 Days)**	**Day 64 (±5 Days)**	**Day 85 (±5 Days)**	**Day 113 *(± 3 Days)***
PTE/AE assessment	X	X	X	X	X	X	X	X
Pregnancy testing and pregnancy avoidance counseling (*e,f*)	X	X	X		X		X	
Access IxRT for subject ID/ medication ID/subject status	X	X	X		X		X	
Dispense study drug		X	X		X			
Dose adjustment (as needed) (g)			X		X			

	Screening	Treatment						Telephone Follow-up
	Visit 1 (a)	Baseline Visit 2 (a) Day 1	Visit 3 Wk 2	Telephone Contact Visit 4 Wk 4	Visit 5 Wk 6	Telephone Contact Visit 6 Wk 9	End of Study Visit 7 Wk 12 /Early Termination	Visit 8 Wk 16
	Days -21 up to -1	Day 1	Day 15 (±3 Days)	Day 29 (±3 Days)	Day 43 (±5 Days)	Day 64 (±5 Days)	Day 85 (±5 Days)	Day 113 *(± 3 Days)*
Study drug return/accountability/ compliance			X		X		X	

(a) Screening and Baseline Visits may be combined as determined appropriate per the investigator. Any procedure that is to be performed at both visits should only be conducted once for a combined visit.
(b) UDS to be done at Screening and Baseline. UDS kits will be supplied by the sponsor for the testing at the clinic. UDS results must be negative. This includes benzodiazepines and opiates for which there is no prescription (including oxycodone) at Screening and Baseline. Results must be confirmed prior to conducting the Baseline Visit.
(c) Height at Screening only; weight at Screening, Baseline, and Week 12.
(d) Subjects who signed an informed consent for pharmacogenomic testing will have blood samples for PGx analysis and these will be collected as follows: 2×3 mL for DNA on Day 1; 2×2.5 mL for RNA predose on Day 1 and at Week 12 (Visit 6).
(e) Urine hCG pregnancy tests will be performed at Screening and Baseline and for all other visits during the Treatment Period for women of childbearing potential only. Serum hCG pregnancy tests will be performed at Baseline and End of Study/Early Termination visits for all females. For combined Screening and Baseline Visits, there will be 1 urine and 1 serum hCG. Subjects may be enrolled with a negative urine hCG; however if the serum hCG is positive the subject must be withdrawn from study drug immediately and withdrawn from the study as soon as possible.
(f) Subject who are women of childbearing potential 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 of pregnancy and donation of ova during the course of the study and for 4 weeks after the last dose of study drug.
(g) Dose adjustments should occur during regularly scheduled visits, or subjects should return for an Unscheduled Visit.

Revised Text

	Screening	Treatment						Telephone Follow-up
	Visit 1 (a)	Baseline Visit 2 (a) Day 1	Visit 3 Wk 2	Telephone Contact Visit 4 Wk 4	Visit 5 Wk 6	Telephone Contact Visit 6 Wk 9	End of Study Visit 7 Wk 12 /Early Termination	Visit 8 Wk 16
	Days -21 up to -1	Day 1	Day 15 (±3 Days)	Day 29 (±3 Days)	Day 43 (±5 Days)	Day 64 (±5 Days)	Day 85 (±5 Days)	Day 113 (± 7 Days)
Document factors for determining a change/discontinuation from prior antidepressant (e)	**X**							
PTE/AE assessment	X	X	X	X	X	X	X	X
Pregnancy testing and pregnancy avoidance counseling (**f,g**)	X	X	X		X		X	

	Screening	Treatment						Telephone Follow-up
	Visit 1 (a)	Baseline Visit 2 (a) Day 1	Visit 3 Wk 2	Telephone Contact Visit 4 Wk 4	Visit 5 Wk 6	Telephone Contact Visit 6 Wk 9	End of Study Visit 7 Wk 12 /Early Termination	Visit 8 Wk 16
	Days -21 up to -1	Day 1	Day 15 (±3 Days)	Day 29 (±3 Days)	Day 43 (±5 Days)	Day 64 (±5 Days)	Day 85 (±5 Days)	Day 113 (± 7 Days)
Access IxRT for subject ID/ medication ID/subject status	X	X	X		X		X	
Dispense study drug		X	X		X			
Dose adjustment (as needed) (**h**)			X		X			
Clinician and subject satisfaction with change in antidepressant							**X**	
Clinician and subject satisfaction with GAS approach							**X**	
Study drug return/accountability/ compliance			X		X		X	

(a) Screening and Baseline Visits may be combined as determined appropriate per the investigator. Any procedure that is to be performed at both visits should only be conducted once for a combined visit.
(b) UDS to be done at Screening and Baseline. UDS kits will be supplied by the sponsor for the testing at the clinic. UDS results must be negative. This includes benzodiazepines and opiates for which there is no prescription (including oxycodone) at Screening and Baseline. Results must be confirmed prior to conducting the Baseline Visit.
(c) Height at Screening only; weight at Screening, Baseline, and Week 12.
(d) Subjects who signed an informed consent for PGx testing will have blood samples for PGx analysis and these will be collected as follows: 2×3 mL for DNA on Day 1; 2×2.5 mL for RNA predose on Day 1 and at Week 12 (Visit 6).
(e) To be collected at Screening or combined Screening/Baseline Visit.
(f) Urine hCG pregnancy tests will be performed at Screening and Baseline and for all other visits during the Treatment Period for women of childbearing potential only. Serum hCG pregnancy tests will be performed at Baseline and End of Study/Early Termination visits for all females. For combined Screening and Baseline Visits, there will be 1 urine and 1 serum hCG. Subjects may be enrolled with a negative urine hCG; however if the serum hCG is positive the subject must be withdrawn from study drug immediately and withdrawn from the study as soon as possible.
(g) Subject who are women of childbearing potential 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 of pregnancy and donation of ova during the course of the study and for **30 days** after the last dose of study drug.
(h) Dose adjustments should occur during regularly scheduled visits, or subjects should return for an Unscheduled Visit.

Rationale for Amendment

Documentation of antidepressant change, and satisfaction with change in treatment was noted in Section 9.3, but was not listed in the table of procedures in error. Clinician and subjects satisfaction with GAS is being added to assess the GAS approach in clinical practice and to guide future GAS work. Footnote e was added and subsequent footnotes were renumbered. Footnote g was edited to match inclusion criteria and section 9.1.10.

Page 80, Appendix C, Elements of the Subject Informed Consent, Item #25

Existing Text

Female women of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 5 half lives PLUS *4 weeks* after last dose. Regular pregnancy tests will be performed throughout the study for all female women of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

Revised Text

Female women of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 5 half lives PLUS **30 days** after last dose. Regular pregnancy tests will be performed throughout the study for all female women of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

Rationale for Amendment

To keep language consistent with inclusion criteria**.**

Amendment 1 An Open-Label, Single-Arm, Multicenter, Prospective, Phase 4, Interventional, Flexible Dose Study to Evaluate the Effectiveness of Vortioxetine on Goal Achievement After a Change in Antidepressant Medication for the Treatment of Subjects With Major Depressive Disorder

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Biostatistics Approval	22-Aug-2017 17:32 UTC
	Pharmacovigilance Approval	22-Aug-2017 17:36 UTC
	Clinical Operations Approval	22-Aug-2017 22:19 UTC
	Clinical Science Approval	22-Aug-2017 22:53 UTC