Title: Title: Randomized, Double-Blind, Parallel Group, Placebo- and Active-Controlled, Phase 4 Study Evaluating the Effect of Vortioxetine 10 and 20 mg/day vs Paroxetine 20 mg/day on Sexual Functioning in Healthy Subjects

NCT Number: NCT02932904

Protocol Approve Date: 10 January 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

A Randomized, Double-Blind, Parallel Group, Placebo- and Active-Controlled, Phase 4 Study Evaluating the Effect of Vortioxetine 10 and 20 mg/day vs Paroxetine 20 mg/day on Sexual Functioning in Healthy Subjects

Effect of Vortioxetine, Paroxetine, and Placebo on Sexual Functioning in Healthy Volunteers

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015		
Study Number:	Vortioxetine-4001		
IND Number:	76,307	**EudraCT Number:**	Not applicable
Compound:	Vortioxetine		

Amendment History:

Date	Amendment Number	Amendment Type	Region
11 July 2016	Initial version	Not applicable	United States
10 January 2017	01	Substantial	United States

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center Americas, Inc. (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	North America (United States) Contact
Serious adverse event and pregnancy reporting	Takeda Development Center Americas, Inc. Pharmacovigilance Department PPD
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 Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD

Date

PPD

Date

PPD

Date

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 Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Appendix B – Responsibilities of the Investigator.

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 01 Summary of Changes

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

The primary purpose of this amendment is to update the protocol regarding eligibility criteria. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in Appendix F, including detailed rationale. The following is a summary of the changes made in the amendment:

1. Clarify inclusion and exclusion criteria.
2. Update, correct, or clarify excluded medications and treatments.
3. Add that psychiatric history will be assessed as well as medical history.
4. Add instructions on the order in which the scales Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) and Patient Global Impression of Improvement (PGI-I) should be completed.
5. Update personnel changes.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Vortioxetine	
Title of Protocol: A Randomized, Double-Blind, Parallel Group, Placebo- and Active-Controlled, Phase 4 Study Evaluating the Effect of Vortioxetine 10 and 20 mg/day vs Paroxetine 20 mg/day on Sexual Functioning in Healthy Subjects	**IND No.:** 76,307	**EudraCT No.:** Not applicable
Study Number: Vortioxetine-4001	**Phase:** 4	

Study Design:

This is a phase 4, multicenter, randomized, double-blind, placebo- and active-controlled (paroxetine), 4-arm, parallel group, fixed-dose study comparing the effect of vortioxetine (10 and 20 mg once daily [QD]) vs paroxetine (20 mg QD) on sexual functioning after 5 weeks of treatment in healthy adult men and women. This outpatient study will be conducted at approximately 15 sites in North America. Men and women will be enrolled in approximately equal proportions (ie, 50% men and 50% women, overall). Enrollment will be capped for each sex when the enrollment target has been met for that sex stratum.

Subjects will enter a Screening Period of up to 4 weeks. At Baseline (Day 0), eligible subjects will be equally (1:1:1:1) randomized to double-blind vortioxetine 10 mg, vortioxetine 20 mg, paroxetine 20 mg, or placebo and will be treated for 5 weeks. Randomization will be stratified by sex. Subjects allocated to vortioxetine 20 mg will initiate treatment at 10 mg/day for the first week. Subsequently, the dose will be increased to 20 mg/day and remain at 20 mg/day until study completion. Subjects allocated to vortioxetine 10 mg will initiate treatment at 10 mg/day and remain at 10 mg/day until study completion. Subjects allocated to paroxetine 20 mg will initiate treatment at 20 mg/day and remain at 20 mg/day until study completion. Subjects will be instructed to take their first dose of study drug the day after Baseline on Day 1, preferably in the morning. After randomization, subjects will be seen for weekly visits and receive a follow-up safety contact by telephone 2 weeks after the end of double-blind treatment. At the end of 5 weeks of treatment, or at early termination (ET), all subjects will abruptly discontinue study drug.

Sexual functioning will be assessed at each study visit using the CSFQ-14 (primary variable). The PGI-I scale will be administered at each study visit except at Screening and Baseline. Signs of suicidal risk will be assessed at each study visit using the Columbia-Suicide Severity Rating Scale (C-SSRS) and the investigator's clinical judgment. Safety will be assessed throughout the study. A total of 6 sparse pharmacokinetic (PK) samples (trough samples) will be collected to measure plasma vortioxetine or paroxetine concentrations at Weeks 3, 4, and 5/ET (2 samples at each time point). A pharmacogenomic (PGx) blood sample for deoxyribonucleic acid (DNA) isolation will be collected predose at Baseline (Day 0), and 2 PGx blood samples for ribonucleic acid (RNA) isolation will be collected predose at Baseline (Day 0) and also at Week 5/ET (ie, 4 samples per subject).

Primary Objective:

- To evaluate the effect of vortioxetine (10 and 20 mg QD) vs paroxetine 20 mg QD on sexual functioning in healthy subjects after 5 weeks of double-blind treatment.

Secondary Objectives:

- To evaluate the effect of vortioxetine (10 and 20 mg QD) vs paroxetine 20 mg QD on sexual functioning in healthy subjects throughout the 5-week double-blind Treatment Period.
- To evaluate the effect of paroxetine (20 mg QD) vs placebo on sexual functioning in healthy subjects throughout the 5-week double-blind Treatment Period.
- To evaluate the effect of vortioxetine (10 and 20 mg QD) vs placebo on sexual functioning in healthy subjects throughout the 5-week double-blind Treatment Period.

Additional Objectives:

- To evaluate the effects of vortioxetine (10 and 20 mg QD) vs paroxetine (20 mg QD) on additional parameters of sexual functioning.
- To evaluate the effect of vortioxetine (10 and 20 mg QD) and paroxetine (20 mg QD) vs placebo on additional parameters of sexual functioning.
- To evaluate the subject's perception of sexual functioning.
- To assess the treatment effect (vortioxetine, paroxetine, or placebo) on suicidal ideation and behavior.

Safety Objective:

- To evaluate the safety and tolerability of vortioxetine (10 and 20 mg QD) and paroxetine (20 mg QD) vs placebo.

Subject Population: Healthy men and women aged 18 to 40 years, inclusive.

Number of Subjects:	**Number of Sites:**
Per each of 4 treatment arms: 88 Estimated total: 352	Approximately 15 sites in North America
Dose Levels: • Vortioxetine 10 mg • Vortioxetine 20 mg • Paroxetine 20 mg • Placebo	**Route of Administration:** Oral
Duration of Treatment: Single dose QD for 5 weeks	**Period of Evaluation:** 5 weeks, plus a 2-week follow-up

Main Criteria for Inclusion:

- The subject is a healthy male or female aged 18 to 40 years, inclusive.
- The subject has been in a steady relationship for ≥3 months and plans to remain in that relationship for the duration of the study, and is currently sexually active (≥2 times per week). Note: Partners are not allowed to enroll in this trial.
- The subject has a body mass index of 18 to 35 kg/m2, inclusive, at the Screening and Baseline Visits.
- If female, the subject has a regular menstrual cycle (note: amenorrhea resulting from hormonal contraceptives is not exclusionary).
- The subject has normal sexual functioning, as defined by a CSFQ-14 total score >47 (men) or >41 (women) at the Screening and Baseline Visits.
- If female, the subject taking allowed hormonal contraceptives is on a stable dose for ≥3 months prior to the Baseline Visit and continues on the stable dose for the duration of the study.

Main Criteria for Exclusion:

- The subject has a clinically significant unstable illness or a history of depression or any other psychiatric illness.
- The subject is positive for hepatitis B surface antigen, anti–hepatitis C virus antibodies, or human immunodeficiency virus at the Screening Visit or has any known sexually transmitted diseases.
- The subject has a known history of or currently has increased intraocular pressure or is at risk of acute narrow-angle glaucoma.
- The subject has a significant risk of suicide according to the investigator's clinical judgment, or has made a suicide attempt at any time.
- The subject has current sexual dysfunction, or a history of a diagnosis or treatment of sexual dysfunction.

- The subject has had a surgical or medical procedure on reproductive/genitourinary organs (excluding uncomplicated cesarean section (C-section), vasectomy, and tubal ligation that do not impact sexual function).
- If female, the subject has polycystic ovarian syndrome.
- The subject has hypogonadism or has a free testosterone value outside the normal range at the Screening Visit that is indicative of hypogonadism.
- The subject has a history of or current alcohol or other substance abuse or dependence (according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised [DSM-IV-TR] criteria).
- The subject has habitual tobacco or other nicotine usage (equivalent to ≥10 cigarettes per day).

Main Criteria for Evaluation and Analyses:

Primary Endpoint

- Change from Baseline in the CSFQ-14 total score difference for vortioxetine vs paroxetine after 5 weeks of treatment.

Secondary Endpoints

- Change from Baseline in the CSFQ-14 total score difference for vortioxetine vs paroxetine at each visit assessed.
- Change from Baseline in CSFQ-14 total score difference for paroxetine vs placebo at each visit assessed.
- Change from Baseline in CSFQ-14 total score difference for vortioxetine vs placebo at each visit assessed.
- Percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any visit during the 5-week double-blind Treatment Period.
- Change from Baseline in CSFQ-14 subscales 5 dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation) and 3 phases of the sexual response cycle (desire, arousal, and orgasm/completion) at each visit assessed.

Additional Endpoints

- Percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any 2 consecutive visits during the 5-week double-blind Treatment Period.
- Time to sexual dysfunction as assessed by the CSFQ-14.
- Percentage of subjects with a shift in the CSFQ-14 from normal (ie, CSFQ-14 total score >47 for men and >41 for women) at Baseline to abnormal (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at each visit assessed.
- Percentage of subjects showing decreased sexual function (ie, negative responders) according to the CSFQ-14 (ie, CSFQ-14 total score decrease from Baseline ≥3) at each visit assessed.
- PGI-I score at each visit assessed.
- C-SSRS at each visit assessed.

Safety Assessments

- Adverse events (AEs), vital signs, clinical laboratory tests, weight, and physical examinations.

Statistical Considerations:

Primary Analysis

Mean change from Baseline in the CSFQ-14 total score difference for vortioxetine vs paroxetine after 5 weeks of treatment will be the primary endpoint. The primary analysis will be based on analysis of covariance (ANCOVA) using the last observation carried forward (LOCF) technique, with treatment, center, and sex as fixed factors, and baseline CSFQ-14 total score as covariate. The comparisons will be between each vortioxetine dose (10 or 20 mg) and paroxetine, and both statistical tests will be 2-sided. The Holm-Bonferroni method will be used to adjust for multiplicity and control the familywise type I error rate at a significance level of 0.05. If the smaller of the 2 p-values is <0.025, significance is obtained for the associated vortioxetine dose and the other dose will then be evaluated at a 0.05 significance level. Although vortioxetine will be compared with paroxetine in the primary analysis, paroxetine

will also be compared with placebo to validate the study.

Secondary Analyses

Change from Baseline in CSFQ-14 total score for vortioxetine vs paroxetine, paroxetine vs placebo, and vortioxetine vs placebo at each visit will also be analyzed using ANCOVA and LOCF, with treatment, center, and sex as fixed factors, and baseline CSFQ-14 total score as covariate. Similar analyses will also be performed for the male and female subgroups. Comparisons to placebo will be made at the significance level of 0.05 outside of multiplicity control.

The percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any visit (using LOCF) during the double-blind Treatment Period will be analyzed by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

Change from Baseline in CSFQ-14 subscales 5 dimensions and 3 phases of the sexual response cycle will be analyzed at all visits using ANCOVA and LOCF similar to the primary analysis.

Additional Analyses

The percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any 2 consecutive visits (using LOCF) during the double-blind Treatment Period will be analyzed by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

Time to sexual dysfunction as assessed by the CSFQ-14 will be analyzed using a Cox model with an exact method to handle ties, with treatment and sex as factors.

CSFQ-14 shift from normal (ie, CSFQ-14 total score >47 for men and >41 for women) at Baseline to abnormal (ie, CSFQ-14 total score ≤47 for men and ≤41 for women), and CSFQ-14 negative responders (decrease from Baseline in CSFQ-14 total score ≥3) will be analyzed at all visits by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

PGI-I will be analyzed by study visit using ANCOVA and LOCF, with treatment, center, and sex as fixed factors.

C-SSRS will be summarized by study visit for each treatment group using descriptive statistics.

Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term for the double-blind Treatment Period and the entire study. AEs that were reported more than once by a subject during the double-blind Treatment Period will be counted only once for that subject at the maximum severity.

Absolute values and changes from Screening/Baseline for clinical laboratory tests, vital signs, and weight will be summarized for each treatment group using descriptive statistics. Clinical laboratory test and vital sign results that are outside the normal ranges and potentially clinically significant will be flagged and tabulated. Physical examination findings will also be summarized for each treatment group.

PK Analysis

Plasma concentrations of vortioxetine and paroxetine will be presented in the data listings. A population PK analysis will only be conducted if deemed necessary. If this analysis is conducted, the results will be reported in a separate population PK report.

PGx Analysis

DNA samples may be used to understand the mode of action of vortioxetine, and RNA samples may be used for subsequent pathway analysis. Also, since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development using stored samples.

Sample Size Justification:

Approximately 352 male and female subjects will be randomized to 4 treatment arms.

Assuming an SD of 8.5 for the change from Baseline in CSFQ-14 total score, a total of 352 male and female subjects (88 subjects per arm) is sufficient to achieve ≥80% power to detect a difference of 4.0 for vortioxetine 20 mg vs paroxetine 20 mg or for vortioxetine 10 mg vs paroxetine 20 mg by a 2-sample t-test with a 0.025 2-sided significance level. Given the proposed Holm-Bonferroni method for multiplicity control, the power to achieve the significance for each vortioxetine dose is approximately 85%.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 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	5-hydroxytryptamine (serotonin)
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
BMI	body mass index
C-section	cesarean section
CFR	Code of Federal Regulations
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	deoxyribonucleic acid
DRESS	drug reaction with eosinophilia and systemic symptoms
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised
ECG	electrocardiogram
eCRF	electronic case report form
ET	Early Termination
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HbA1c	glycosylated hemoglobin
HBr	hydrobromide
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ID	identification
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
K2EDTA	potassium ethylenediamine tetraacetic acid
LFT	liver function tests
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder

OE	overencapsulated
PGI-I	Patient Global Impression of Improvement
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PPS	per-protocol analysis set
PTE	pretreatment event
QD	once daily
RCF	relative centrifugal force
RNA	ribonucleic acid
SAE	serious adverse event
SJS	Stevens-Johnson syndrome
SMS	short message service
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
T4	thyroxine
TEN	toxic epidermal necrolysis
TESD	treatment-emergent sexual dysfunction
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

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

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

Unfortunately, most of the currently available antidepressants produce sexual dysfunction in men and women and affect all phases of sexual activity by decreasing desire, arousal, orgasm, and ejaculation [3-7]. Such side effects affect the patient's quality of life, can lead to therapeutic noncompliance, and often interfere with recovery from a depressive episode [4,8-10]. In a study conducted by Hu et al (2004) [11], patients receiving antidepressant treatment were asked to rank which of the side effects they experienced were the most bothersome. In this population, sexual dysfunction was ranked as the most bothersome adverse event (AE), followed by drowsiness/fatigue, weight gain, and insomnia.

Despite being common, antidepressant-related sexual dysfunction is one of the most under reported AEs [11,12]. In a study by Montejo-Gonzalez et al (1997), only 14% of the patients spontaneously reported sexual-related AEs; when elicited by direct question, however, as many as 58% of these patients reported sexual dysfunction [13].

Using an objective measurement to assess the rate of sexual dysfunction in a sample of individuals receiving antidepressant monotherapy, Clayton and Montejo (2006) [14] found that the prevalence of sexual dysfunction was on average 24% (ranging from 7% to 30%, depending on the medication).

Vortioxetine is an antidepressant agent approved in 66 countries worldwide, including in the United States (US) and the European Union since 2013, for treatment of MDD. It differs from preexisting antidepressants in that it combines 2 pharmacological modes of action: direct modulation of 5-hydroxytryptamine (5-HT) (serotonin) receptor activity and inhibition of the 5-HT transporter. Vortioxetine is an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors, and an inhibitor of the 5-HT transporter [15,16].

During the clinical development program, the efficacy, safety, and tolerability of vortioxetine in subjects with MDD was evaluated at doses from 1 to 20 mg/day 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 evaluated. The efficacy of vortioxetine in the treatment of subjects with MDD was established in 6 randomized, double-blind, placebo-controlled, fixed-dose, 6- to 8-week 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 [17].

The long-term efficacy and maintenance of effect of vortioxetine treatment at doses of 5 and 10 mg/day have been previously established in subjects with MDD [18].

4.2 Rationale for the Proposed Study

Treatment with antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), may be associated with sexual dysfunction including AEs at virtually all phases of sexual response (ie, desire, arousal, and orgasm), which can frequently result in poor treatment compliance and even antidepressant treatment discontinuation [5]. Results from phase 3 studies in acute depressed subjects indicate that vortioxetine is associated with less treatment-emergent sexual dysfunction (TESD) when compared with duloxetine, and is similar to placebo at the 5 and 10 mg doses, as assessed by data collected prospectively utilizing the Arizona Sexual Experiences Scale (ASEX) and by spontaneous reports of AEs during 8 weeks of treatment [17].

A subsequent study was conducted to evaluate the effects of vortioxetine in improving antidepressant-associated sexual dysfunction compared with another antidepressant using an objective measure, the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14). In this study, adult subjects with MDD whose depressive symptoms were well treated with 1 of 3 SSRIs, citalopram, sertraline, or citalopram, but who had abnormal sexual functioning, as assessed by the CSFQ-14, which in the investigator's opinion was attributed to the subject's current SSRI treatment, were switched to vortioxetine or escitalopram. Vortioxetine was statistically significantly superior to escitalopram in improving SSRI-induced sexual dysfunction as measured by the CSFQ-14 total score at Week 8 [19].

The objective of the current study is to further evaluate the effects of vortioxetine on sexual functioning as compared with paroxetine, an SSRI known to cause sexual dysfunction, in healthy subjects after 5 weeks of treatment.

Pharmacogenomic (PGx) analysis may be conducted to evaluate the contribution of genetic variance on drug response (eg, safety and tolerability). The sampling of whole blood for PGx analysis is mandatory; every subject must consent to this procedure to participate in this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the effect of vortioxetine (10 and 20 mg once daily [QD]) vs paroxetine 20 mg QD on sexual functioning in healthy subjects after 5 weeks of double-blind treatment.

5.1.2 Secondary Objectives

- To evaluate the effect of vortioxetine (10 and 20 mg QD) vs paroxetine 20 mg QD on sexual functioning in healthy subjects throughout the 5-week double-blind Treatment Period.
- To evaluate the effect of paroxetine (20 mg QD) vs placebo on sexual functioning in healthy subjects throughout the 5-week double-blind Treatment Period.
- To evaluate the effect of vortioxetine (10 and 20 mg QD) vs placebo on sexual functioning in healthy subjects throughout the 5-week double-blind Treatment Period.

5.1.3 Additional Objectives

- To evaluate the effects of vortioxetine (10 and 20 mg QD) vs paroxetine (20 mg QD) on additional parameters of sexual functioning.
- To evaluate the effect of vortioxetine (10 and 20 mg QD) and paroxetine (20 mg QD) vs placebo on additional parameters of sexual functioning.
- To evaluate the subject's perception of sexual functioning.
- To assess the treatment effect (vortioxetine, paroxetine, or placebo) on suicidal ideation and behavior.

5.1.4 Safety Objective

- To evaluate the safety and tolerability of vortioxetine (10 and 20 mg QD) and paroxetine (20 mg QD) vs placebo.

5.2 Endpoints

5.2.1 Primary Endpoint

- Change from Baseline in the CSFQ-14 total score difference for vortioxetine vs paroxetine after 5 weeks of treatment.

5.2.2 Secondary Endpoints

- Change from Baseline in the CSFQ-14 total score difference for vortioxetine vs paroxetine at each visit assessed.

- Change from Baseline in CSFQ-14 total score difference for paroxetine vs placebo at each visit assessed.
- Change from Baseline in CSFQ-14 total score difference for vortioxetine vs placebo at each visit assessed.
- Percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any visit during the 5-week double-blind Treatment Period.
- Change from Baseline in CSFQ-14 subscales 5 dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation) and 3 phases of the sexual response cycle (desire, arousal, and orgasm/completion) at each visit assessed.

5.2.3 Additional Endpoints

- Percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any 2 consecutive visits during the 5-week double-blind Treatment Period.
- Time to sexual dysfunction as assessed by the CSFQ-14.
- Percentage of subjects with a shift in the CSFQ-14 from normal (ie, CSFQ-14 total score >47 for men and >41 for women) at Baseline to abnormal (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at each visit assessed.
- Percentage of subjects showing decreased sexual function (ie, negative responders) according to the CSFQ-14 (ie, CSFQ-14 total score decrease from Baseline ≥3) at each visit assessed.
- Patient Global Impression of Improvement (PGI-I) score at each visit assessed.
- Columbia-Suicide Severity Rating Scale (C-SSRS) at each visit assessed.

5.2.4 Safety Assessments

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

- AEs.
- Vital signs.
- Clinical laboratory tests.
- Weight.
- Physical examinations.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 4, multicenter, randomized, double-blind, placebo- and active-controlled (paroxetine), 4-arm, parallel group, fixed-dose study comparing the effect of vortioxetine (10 and 20 mg QD) vs paroxetine (20 mg QD) on sexual functioning after 5 weeks of treatment in healthy adult men and women. This outpatient study will be conducted at approximately 15 sites in North America. Men and women will be enrolled in approximately equal proportions (ie, 50% men and 50% women, overall). Enrollment will be capped for each sex when the enrollment target has been met for that sex stratum.

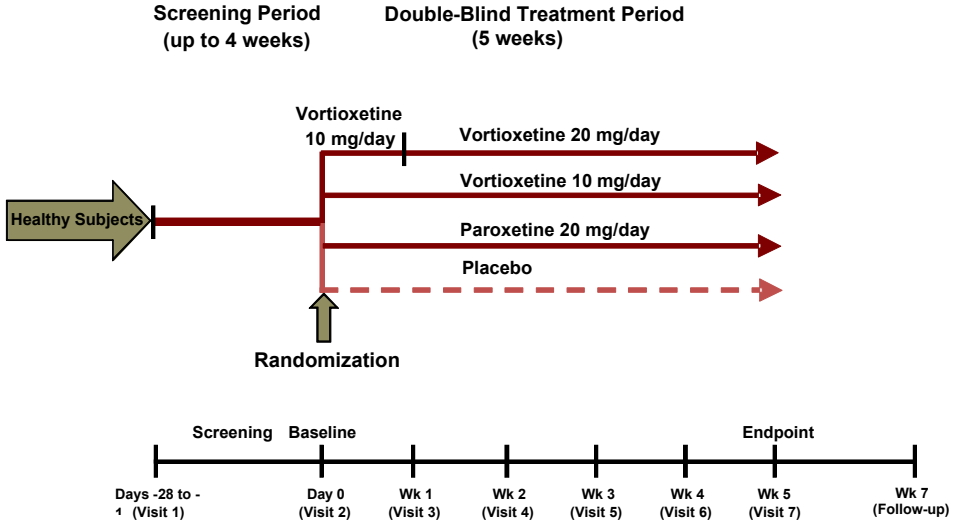
After providing informed consent, subjects will be assessed for study eligibility during a Screening Period of up to 4 weeks. Healthy subjects who have normal sexual functioning (as defined by the CSFQ-14), have been in a steady relationship for ≥3 months, are currently sexually active, and meet all other study entry criteria will be enrolled. At Baseline (Day 0), eligible subjects will be equally (1:1:1:1) randomized to double-blind vortioxetine 10 mg, vortioxetine 20 mg, paroxetine 20 mg, or placebo and will be treated for 5 weeks. Randomization will be stratified by sex. Subjects allocated to vortioxetine 20 mg will initiate treatment at 10 mg/day for the first week. Subsequently, the dose will be increased to 20 mg/day and remain at 20 mg/day until study completion. Subjects allocated to vortioxetine 10 mg will initiate treatment at 10 mg/day and remain at 10 mg/day until study completion. Subjects allocated to paroxetine 20 mg will initiate treatment at 20 mg/day and remain at 20 mg/day until study completion. Subjects will be instructed to take their first dose of study drug the day after Baseline on Day 1, preferably in the morning. After randomization, subjects will be seen for weekly visits and receive a follow-up safety contact 2 weeks after the end of double-blind treatment. At the end of 5 weeks of treatment, or at Early Termination (ET), all subjects will abruptly discontinue study drug.

Sexual functioning will be assessed at each study visit using the CSFQ-14 (primary variable). The PGI-I scale will be administered at each study visit except at Screening and Baseline. Signs of suicidal risk will be assessed at each study visit using the C-SSRS and the investigator's clinical judgment. Safety will be assessed throughout the study. A total of 6 sparse pharmacokinetic (PK) samples (trough samples) will be collected to measure plasma vortioxetine or paroxetine concentrations at Weeks 3, 4, and 5/ET (2 samples at each time point). A PGx blood sample for deoxyribonucleic acid (DNA) isolation will be collected at Baseline (Day 0), and 2 PGx blood samples for ribonucleic acid (RNA) isolation will be collected at Baseline (Day 0) and also at Week 5/ET (ie, 4 samples per subject).

The end of the study is defined as the date the last subject completes the Final Visit (Week 5).

A schematic of the study design is presented in Figure 6.a. A schedule of study procedures is provided in Appendix A.

Figure 6.a Schematic of Study Design



Note: The Follow-up Contact will be conducted by telephone.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

Healthy adult subjects were chosen for inclusion in this study to eliminate the confounding effects on sexual function associated with psychiatric conditions and certain medical conditions. The duration of 5 weeks was selected to allow for sufficient time to evaluate the extent of sexual dysfunction.

Paroxetine was chosen as an active comparator as it is a commonly prescribed SSRI and is known to cause sexual dysfunction, thereby allowing for validation of the study (ie, the level of sexual dysfunction with paroxetine is worse than that of placebo). The level of sexual dysfunction with vortioxetine 10 and 20 mg will also be compared with placebo.

Since study drug compliance is known to impact the study results, a compliance technology vendor, AiCure, will be used to throughout the study to improve study drug compliance. In addition, PK samples will be taken at 3 postbaseline study visits in order to assess plasma concentrations of vortioxetine and paroxetine. The compliance technology and/or PK concentration data will be used to define one or more modified full analysis set populations.

6.2.2 Dose

Subjects will be dosed in accordance with the approved United States Package Insert for vortioxetine; therefore, vortioxetine doses of 10 and 20 mg will be evaluated. Based on prospective evaluation using the ASEX, the incidence of TESD increased as the dose of vortioxetine increases, although never statistically different from placebo; therefore, the chosen

doses of 10 and 20 mg for this study are considered clinically appropriate to evaluate sexual dysfunction as it includes the highest therapeutic dose of vortioxetine.

A paroxetine dose of 20 mg/day was selected as it is the starting dose and lowest effective dose for maintenance treatment for depression. Furthermore, this dose of paroxetine is considered to have the lowest incidence of TESD, but it has also been shown to cause sexual dysfunction in healthy subjects.

6.2.3 Endpoints

The CSFQ-14 is a validated questionnaire designed to assess and detect changes in sexual functioning (see Section 9.1.8.1). In addition, it is recognized by the Food and Drug Administration (FDA) as an accepted tool to assess sexual functioning in clinical studies.

The PGI-I scale is a global self assessment used to rate the response of a subject's condition to therapy or intervention (see Section 9.1.8.2). Although it was originally developed for assessment in women with stress urinary incontinence, it has been used for subject self assessment in other conditions due to its lack of specificity to medical conditions, and its sensitivity to change.

Adequate measures have been implemented in 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 Sites

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

6.3.2 Criteria for Premature Termination or Suspension of 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 Sites

In the event that the sponsor, an institutional review board (IRB), 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 randomization.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is a healthy male or female aged 18 to 40 years, inclusive.
4. The subject has been in a steady relationship for ≥3 months and plans to remain in that relationship for the duration of the study, and is currently sexually active (≥2 times per week). Note: Partners are not allowed to enroll in this trial.
5. The subject has a body mass index (BMI) of 18 to 35 kg/m^2, inclusive, at the Screening and Baseline Visits.
6. If female, the subject has a regular menstrual cycle (note: amenorrhea resulting from hormonal contraceptives is not exclusionary).
7. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to routinely use adequate contraception* from signing of informed consent throughout the duration of the study and for 30 days after the last dose.

   *Definitions and acceptable methods of contraception are defined in Section 9.1.13 and reporting responsibilities are defined in Section 9.1.14.

8. The subject has normal sexual functioning, as defined by a CSFQ-14 total score >47 (men) or >41 (women) at the Screening and Baseline Visits.
9. If female, the subject taking allowed hormonal contraceptives is on a stable dose for ≥3 months prior to the Baseline Visit and continues on the stable dose for the duration of the study.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days or 5 half-lives prior to the Screening Visit, whichever is longer.
2. The subject has received vortioxetine and/or paroxetine in a previous clinical study or as a therapeutic agent.
3. The subject has previously or is currently participating in this study.

4. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
5. The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatological, immunological, hematological, infectious, or dermatological disorder or metabolic disturbance. Note: For the purposes of this study, gastric bypass surgery is considered to be an unstable condition due to the impact on medication absorption.
6. The subject is positive for hepatitis B surface antigen (HBsAg), anti–hepatitis C virus (HCV) antibodies, or human immunodeficiency virus (HIV) at the Screening Visit or has any known sexually transmitted diseases.
7. The subject has 1 or more laboratory value outside the normal range, based on the blood or urine samples taken at the Screening or Baseline Visit, that are considered by the investigator to be clinically significant; or the subject has any of the following values at the Screening or Baseline Visit:
    a) A serum creatinine value >1.5× the upper limits of normal (ULN).
    b) A serum total bilirubin value >1.5×ULN.
    c) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2×ULN.
8. The subject has glycosylated hemoglobin (HbA1c) ≥7% at the Screening Visit.
9. The subject has a clinically significant abnormal electrocardiogram (ECG) at the Screening Visit as determined by the central reader and confirmed as clinically significant by the investigator.
10. The subject has clinically significant abnormal vital signs at the Screening or Baseline Visit as determined by the investigator.
11. The subject has a known history of or currently has increased intraocular pressure or is at risk of acute narrow-angle glaucoma.
12. The subject has a history of depression or any other psychiatric illness including sleep disorders and premenstrual dysphoric disorder.
13. The subject has a significant risk of suicide according to the investigator's clinical judgment, or has made a suicide attempt at any time.
14. The subject has current sexual dysfunction, or a history of a diagnosis or treatment of sexual dysfunction.
15. The subject has had a surgical or medical procedure on reproductive/genitourinary organs (excluding uncomplicated cesarean section (C-section), vasectomy, and tubal ligation that do not impact sexual functioning).

16. If female, the subject has polycystic ovarian syndrome.
17. The subject has hypogonadism or has a free testosterone value outside the normal range at the Screening Visit that is indicative of hypogonadism.
18. The subject has a thyroid-stimulating hormone (TSH) value outside the normal range at the Screening Visit that is deemed clinically significant by the investigator. NOTE: Free thyroxine (T4) will be checked if TSH is out of range. If free T4 is abnormal the subject will be excluded.
19. The subject has a history of hypersensitivity or allergies to vortioxetine or paroxetine or any associated excipients.
20. The subject is required to take ≥1 excluded medication or it is anticipated that the subject will be required to take ≥1 of the excluded medications listed in Section 7.3 during the study.
21. The subject has a history of or current alcohol or other substance abuse or dependence (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised [DSM-IV-TR] criteria).
22. The subject has habitual tobacco or other nicotine-containing product usage (equivalent to ≥10 cigarettes per day).
23. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study, or intending to donate ova during such time period.
24. The subject is found to be a match in the subject registry database with a subject who has participated in another study within the last 30 days (or at any time for an excluded medical or psychiatric condition).
25. The subject has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of sexual functioning, safety, or tolerability.
26. The subject, in the opinion of the investigator, is unlikely to comply with the clinical study protocol or is unsuitable for any reason.

7.3 Excluded Medications and Treatments

A list of excluded medications and treatments is provided in Table 7.a. Use of the excluded medications or treatments is prohibited from the time points specified until completion of all study procedures at the Final Visit/ET Visit, unless approved by the investigator and Takeda on a case-by-case basis.

Table 7.a Excluded Medications and Treatments

Drug Class		Disallowed Prior to/From Baseline and During Study Unless Otherwise Noted	Disallowed (X) During the Study [Sections Without (X) Indicate no Restriction]		
			Chronic Use	Episodic Use	Comments or Exceptions
Any investigational drug		<30 days before Screening or 5 half-lives, whichever is longer	X	X	
Analgesics	Narcotic analgesics	3 months	X	X	
	NSAIDs		X		Up to 2 doses of ibuprofen or naproxen per week allowed. Aspirin is NOT allowed.
	Cox-2 selective inhibitors	3 months	X	X	
	Acetaminophen				
Anorexics		2 weeks	X	X	
Antacids					
Antiacne agents					
Antianginal agents		3 months	X	X	
Antiarrhythmics		3 months	X	X	
Antibiotics					Rifampin is NOT allowed.
Antithrombic and anticoagulant agents		3 months	X	X	
Anticonvulsants		3 months	X	X	
Antidepressants (including MAOIs and RIMAs)		3 months	X	X	
Antidiarrheal agents					
Antifungal agents					
Antihistamines			X	X	Only loratadine, desloratadine, cetirizine, levocetirizine, mizolastine and fexofenadine are allowed.
Antihypertensives		3 months	X	X	
Anti-impotence agents		3 months	X	X	
Antimigraine agents (including triptans and dopamine antagonists)		2 weeks	X	X	
Antinauseants, antiemetics (including dopamine antagonists)		2 weeks	X	X	Only phosphoric acid and bismuth preparations are allowed.
Antineoplastics		3 months	X	X	
Antiobesity agents		2 weeks	X	X	
Antipsoriatic agents					
Antimalarial					
Antipsychotics		3 months (6 months for depot)	X	X	
Antivirals					

Footnotes are on last table page.

Table 7.a Excluded Medications and Treatments (continued)

Drug Class	Disallowed Prior to/From Baseline and During Study Unless Otherwise Noted	Disallowed (X) During the Study [Sections Without (X) Indicate no Restriction]		
		Chronic Use	Episodic Use	Comments or Exceptions
Anxiolytics (including benzodiazepines)	3 months	X	X	
Beta blockers	3 months	X	X	
Cough/cold agents		X		Episodic treatment for up to 1 week is allowed.
Diuretics OTC				
Herbal remedies, which are psychoactive (eg, St. Johns Wort, kava kava, valerian, and ginkgo biloba)	2 weeks	X	X	Melatonin is allowed.
Drugs metabolized by or that inhibit CYP2D6	2 weeks	X	X	Applies to CYP2D6 substrates/inhibitors not mentioned elsewhere in this table.
H2 blockers, proton pump inhibitors				
Hormones		X	X	Chronic and stable thyroid hormone replacement, parathyroid hormone, and its recombinant form (Forteo), contraceptives (oral, patch, injectables, and implants).
Hypoglycemic agents	3 months	X	X	
Hypolipidemics	3 months	X	X	
Insulin	3 months	X	X	
Laxatives				
Mood stabilizers	3 months	X	X	
Psychotropic agents not otherwise specified (including stimulants, narcotics, tryptophan, and dopamine agonists/antagonists)	3 months	X	X	
Sedatives/hypnotics	4 weeks (see comments)	X		From 4 weeks prior to Baseline through end of study, only zolpidem, eszopiclone/zopiclone, zaleplon, and ramelteon allowed up to 2 nights per week and not the night before a study visit.

Footnotes are on last table page.

Table 7.a Excluded Medications and Treatments (continued)

Drug Class		Disallowed Prior to/From Baseline and During Study Unless Otherwise Noted	Disallowed (X) During the Study [Sections Without (X) Indicate no Restriction]		
			Chronic Use	Episodic Use	Comments or Exceptions
Steroids:	Systemic	2 weeks	X	X	Injectable and anabolic steroids are also NOT allowed
	Inhalant				
	Topical				
Vaccines					

COX-2=cyclooxygenase-2, CYP=cytochrome P450, H2 blockers=H2 receptor antagonists (acid reducers), MAOI=monoamine oxidase inhibitor, NSAID=nonsteroidal anti-inflammatory drug, OTC=over the counter, RIMA=reversible inhibitor of monoamine oxidase type A.

The list above does not include all of the excluded medications or supplements. Subjects must be instructed not to take any medications or supplements, including OTC products, throughout the duration of the study without first consulting with the investigator.

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 electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires ET 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, see Section 9.1.12), if the following circumstances occur at any time during study drug treatment:
     - ALT or AST >8×ULN, or
     - ALT or AST >5×ULN and persists for >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 postrandomization 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 wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, 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 9.1.14.
7. Noncompliance with study drug. This includes subjects who did not take the study drug for ≥4 consecutive days and/or are <70% compliant between visits.
8. Other.

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

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 ET Visit. Discontinued or withdrawn subjects will not be replaced. Discontinued or withdrawn subjects will receive a Follow-up Contact.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of 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 encapsulated strengths of 10 and 20 mg.
- Commercial paroxetine tablets in encapsulated strength of 20 mg.
- Matching placebo capsules.

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

The study drug will be packaged in high-density polyethylene bottles with child-resistant closures. Each bottle contains 7 daily doses plus 3 extra capsules for a total of 10 capsules per bottle. The daily dose is 1 capsule by oral administration.

Bottles of overencapsulated (OE) vortioxetine 10 and 20 mg tablets, OE paroxetine 20 mg tablets, and matching placebo capsules will be labeled with a single label and dispensed as double-blind for the 5-week treatment phase. The study drug will be identifiable by a unique medication identification (ID) number that will be assigned by an interactive web response system (IWRS). Each bottle will be labeled with pertinent study information.

8.1.1.1 Study Drug

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

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

Paroxetine 20 mg tablets United States Pharmacopeia (USP) immediate release are commercially available.

8.1.1.2 Sponsor-Supplied Drug

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

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

8.1.2 Storage

Study drug should be stored at 25ºC (77ºF) with excursions permitted between 15ºC and 30ºC (59ºF -86ºF).

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

8.1.3 Dose and Regimen

The investigator or designee should contact the IWRS to register each subject at the initial Screening Visit. At each applicable study visit (Visits 1-5), the investigator or designee should contact the IWRS to receive the appropriate study drug assignment for dispensation. The IWRS will provide the medication ID number for each bottle dispensed at each study visit. The medication ID number assigned should be recorded in the source document.

Subjects assigned to vortioxetine 20 mg will initiate treatment at 10 mg/day for the first week. Subsequently, the dose will be increased to 20 mg/day and remain at 20 mg/day until study completion. Subjects assigned to vortioxetine 10 mg will initiate treatment at 10 mg/day and remain at 10 mg/day until study completion. Subjects assigned to paroxetine 20 mg will initiate treatment at 20 mg/day and remain at 20 mg/day until study completion.

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

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

The daily dose and capsule count that will be provided to each treatment group is described in Table 8.a.

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description
A	Placebo QD	1 placebo capsule
B	10 mg vortioxetine QD	1 OE vortioxetine 10 mg tablet
C	20 mg vortioxetine QD	1 OE vortioxetine 20 mg tablet
D	20 mg paroxetine QD	1 OE paroxetine 20 mg tablet

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 study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on an AE page of the eCRF, as described in Section 10.1.5.3.

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

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

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IWRS at the Screening Visit to obtain the subject number. The investigator or investigator's designee will access the IWRS to randomize the subject into the study should they meet the eligibility requirements. Subjects will be assigned in a 1:1:1:1 ratio to 1 of the 4 treatment arms of vortioxetine 10 mg, vortioxetine 20 mg, paroxetine 20 mg, or placebo. Randomization will be stratified by sex. Men and women will be enrolled in equal proportions (ie, 50% men and 50% women, overall). Enrollment will be capped for each sex when the enrollment target has been met for that sex stratum.

During each IWRS contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. The medication ID number of the study drug to be dispensed will then be provided by the IWRS. If sponsor-supplied drug is lost or damaged, the site can request a replacement from the IWRS (refer to IWRS manual provided separately). At subsequent drug-dispensing visits, the investigator or

designee will again contact the IWRS to request additional study drug for a subject. The medication ID number of the study drug to be dispensed will be provided by the IWRS.

Each subject should be instructed as follows:

- The subject should keep sponsor-supplied drugs in original containers until the time of dosing.
- The subject should take only 1 capsule per day as instructed. If the dose is missed in the morning, it is acceptable to take the dose later in the same day. If the subject misses a dose, he or she should not take twice the dose the next day.
- The subject should store sponsor-supplied drugs according to the label and keep them out of the reach of children.
- The subject is to return sponsor-supplied drugs at each study visit.

8.3 Randomization Code Creation and Storage

Takeda randomization personnel or designee will generate the randomization schedule for the study; an IWRS will be used in a centralized fashion for subject randomization and study drug assignments with stratification by sex. All randomization information will be stored in a secured area, accessible only by authorized personnel. Target randomization is 50% men and 50% women; enrollment for each sex will be monitored and will be discontinued once the appropriate numbers of subjects have been enrolled for a sex stratum.

Subjects will be assigned in a 1:1:1:1 ratio, within each sex stratum, to the 4 treatment arms of vortioxetine 10 mg, vortioxetine 20 mg, paroxetine 20 mg, or placebo. Subject randomization across treatments and sex will be balanced at the study level.

8.4 Study Drug Blind Maintenance

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

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the sponsor/designee should be notified before the study drug blind is broken. If a medical emergency requiring unblinding occurs, the investigator (or designee) at the site will contact the sponsor or designee (see medical monitor contact information listed in Section 1.1) to assess the necessity to break the study drug blind.

For unblinding a subject, the study drug blind can be obtained by accessing the IWRS. The sponsor/designee must be notified immediately if the study drug blind is broken. The date, time,

and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

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

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

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

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

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by recording in the IWRS. If there are any discrepancies between the packing list vs 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 the following:

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

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

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

The investigator or designee must record the current inventory of all sponsor-supplied drugs (vortioxetine 10 and 20 mg, paroxetine 20 mg, and placebo) 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.

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

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.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures to be performed 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.

PGx informed consent is a component of the overall study informed consent. Collection of PGx blood samples is mandatory for each subject (see Section 9.1.15).

The Subject Database Authorization will also be a component of the overall study informed consent (see Section 9.1.2).

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

9.1.2 Subject Database and Authorization

Clinical trial subject registries seek to reduce subjects from enrolling into multiple clinical trials by identifying duplicates before enrollment. This study will utilize one or more subject registry databases. At the time of providing the informed consent for the study, the investigator or designee will explain to the subject the IRB-approved Subject Database Authorization and witness the signature.

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

9.1.3 Demographics, Medical History, Psychiatric History, and Medication History Procedure

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

Medical history 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 stopped at or prior to signing of informed consent. Ongoing medical and/or psychiatric conditions are considered concurrent conditions (see Section 9.1.11).

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

9.1.4 Physical Examination Procedure

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

All subsequent physical examinations should assess clinically significant changes from the assessment prior to the first dose of study drug (baseline examination).

9.1.5 Weight, Height, and BMI

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

BMI = weight (kg)/[height (m)]^2

Note that although height is measured in centimeters, the BMI formula uses meters for height; meters can be determined by dividing centimeters by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then BMI=79.2/1.76^2=25.56818 kg/m^2.

BMI values will be reported to 1 decimal place by rounding. The above value should be captured as 25.6 kg/m^2 in the database.

9.1.6 Vital Sign Procedure

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

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

9.1.7 ECG Procedure

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

trace over time. Requirements for the ECG equipment and procedure for collecting and transferring information to the central reader will be provided in the site manual.

9.1.8 Sexual Functioning Assessments

9.1.8.1 CSFQ-14

The CSFQ-14 is a structured self-reported questionnaire designed to measure illness- and medication-related changes in sexual functioning that consists of 14 items measuring sexual functioning as a total score (14 items) and on the subscales of pleasure (1 item), desire/frequency (2 items), desire/interest (3 items), arousal (3 items), and orgasm (3 items). Two additional items are included in the total score, but do not map to a specific phase of the sexual response cycle. Lower scores are associated with worsened sexual functioning [20]. The subject should complete the CSFQ-14 scale before the PGI-I scale at all post-baseline visits.

9.1.8.2 PGI-I Scale

The PGI-I scale is a global self assessment used to rate the response of a subject's condition to therapy or intervention. It consists of one question that asks the subject to rate their current condition compared to how it was prior to beginning treatment on a scale of 1 (very much better) to 7 (very much worse). It was originally developed for assessment in women with stress urinary incontinence [21]. However, due to its lack of specificity for medical conditions, and its sensitivity to change, it has been used for subject self assessment in other conditions. The subject should complete the CSFQ-14 scale before the PGI-I scale at all post-baseline visits.

9.1.9 C-SSRS

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 study of centrally-acting drugs [22,23]. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.

9.1.10 Documentation of Concomitant Medications

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

9.1.11 Documentation of Concurrent Medical and/or Psychiatric Conditions

Concurrent medical and/or psychiatric conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant

laboratory, ECG, or physical examination abnormalities noted at the screening or baseline examination. The condition (ie, diagnosis) should be described.

9.1.12 Procedures for Clinical Laboratory Samples

Laboratory samples will be collected at the time points stipulated in the Schedule of Study Procedures (Appendix A). The maximum volume of blood collected at any single visit is approximately 25 mL, and the approximate total volume of blood for the study is 88 mL (Table 9.a). Samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a Approximate Blood Volume

Sample Type	Volume per Sample	Number of Samples (a)				Total Volume
		Screening Period	Baseline	Treatment Period	Final Visit/ ET Visit	
HBsAg, HCV, HIV	6 mL	1	---	---	---	6 mL
Free testosterone, TSH/free T4, HbA1c	2 mL	3 (b)	---	---	---	6 mL
Serum chemistry tests (c)	6 mL	1	1	---	1	18 mL
Hematology tests	2 mL	1	1	---	1	6 mL
PK analysis (d)	6 mL	---	---	4	2	36 mL
DNA isolation	6 mL	---	1	---	---	6 mL
RNA isolation	2.5 mL	---	2	---	2	10 mL
Total Blood Volume						**88 mL**

--- =not applicable.
(a) Does not include blood draws at any unscheduled visits.
(b) One 2 mL blood sample for each test.
(c) Includes serum pregnancy test for women of childbearing potential.
(d) For measurement of vortioxetine or paroxetine concentrations in plasma.

The clinical laboratory tests to be performed are listed in Table 9.b.

Table 9.b Clinical Laboratory Tests

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

Other:

Serum	Urine
HIV (a)	Drug screen: anabolic steroids, amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, ethyl alcohol, methadone, phencyclidine, propoxyphene, methaqualone, and oxycodone (f)
HBsAg (a)	
HCV (a)	
TSH, free T4 (e)	
Free testosterone (a)	
Female subjects of childbearing potential	Female subjects of childbearing potential
Beta hCG (for pregnancy) (a)	Beta hCG (for pregnancy) (g)

GGT=γ-glutamyl transferase, hCG=human chorionic gonadotropin, RBC=red blood cell, WBC=white blood cell.
(a) To be performed at Screening only.
(b) To be performed only if total bilirubin ≥2 mg/dL.
(c) Microscopic examination of sediment to be performed only if the dipstick results are positive.
(d) To be performed only if subjects experience ALT or AST >3×ULN as part of the required follow-up laboratory tests.
(e) TSH to be measured at Screening to exclude subjects with clinically significant thyroid dysfunction (hyperthyroidism or hypothyroidism), which may impact sexual functioning. If TSH value is outside the normal range, free T4 will be measured.
(f) To be performed at Screening, Baseline, and at any time at the discretion of the investigator.
(g) To be performed at all study visits except Screening.

The central laboratory will perform all clinical laboratory tests with the exception of the urine pregnancy (hCG) tests, which will be performed at the study site. The clinical laboratory test results will be returned to the investigator, who will be responsible for filing and reviewing these

results together with the data in the eCRF. The investigator is responsible for recording the interpretation of clinical significance of any abnormal laboratory results in the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

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

(Please refer to Section 7.4 for discontinuation criteria, and Section 10.1.5.2 for the appropriate guidance on reporting of abnormal LFTs in relation to ALT or AST >3×ULN in conjunction with total bilirubin >2×ULN.)

If the ALT or AST remains elevated >3×ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and 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 for reporting requirements).

For subjects with positive drug screen results, confirmation testing should be performed (except for ethyl alcohol). If methadone testing is to be performed after vortioxetine administration, confirmation testing must be performed as false positives may occur.

9.1.13 Contraception and Pregnancy Avoidance Procedure

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

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as ≥1 year since last regular menses with a follicle-stimulating hormone level >40 IU/L or ≥5 years since last regular menses, confirmed before any study drug is implemented).

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

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

Barrier methods (each time the subject has intercourse):

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

Intrauterine devices (IUDs):

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

Hormonal contraceptives:

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

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

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

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

9.1.14 Pregnancy

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

If the pregnancy occurs during administration of active study drug, eg, after the Baseline Visit or within 30 days of the last dose of active study drug, 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. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

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

9.1.15 PGx Sample Collection

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 to how the drug is broken down or how the drug affects the body. This is called a "PGx research study." Specific purposes of such a study include the following:

- 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 drugs, and for improving the efficiency, design, and study methods of future research studies.

In the current study, collection of PGx blood samples is mandatory for each subject. PGx informed consent is a component of the overall study informed consent.

One 6-mL whole blood sample for DNA isolation will be collected predose at Baseline (Day 0) from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K_2EDTA) spray-coated tubes, and stored under frozen conditions. If necessary and feasible, a second aliquot of blood may be collected if isolation of DNA from the first sample was not successful or possible. In addition, if the whole blood sample for DNA isolation is not collected at Baseline, it may be collected at any point in the study.

Two 2.5-mL whole blood samples for RNA isolation will be collected predose at Baseline (Day 0) and also at Week 5/ET from each subject in the study (ie, 4 samples per subject), into a PaxGene tube.

Each PGx sample for a study subject should be identifiable on the requisition form with a 8-digit subject ID number (the 5-digit site number plus the 3-digit subject number).

The samples will be stored for no longer than 15 years after completion of the vortioxetine study. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. "Stored samples" are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of study drug or related drugs.

Detailed instructions for the handling and shipping of samples are provided in the study laboratory manual.

9.1.16 PK Sample Collection and Analysis

9.1.16.1 Collection of Plasma for PK Sampling

A total of six 6-mL PK blood samples (trough samples) will be collected from each subject at 3 separate study visits (2 samples at each time point at Weeks 3, 4, and 5/ET). At Week 5/ET, the blood sample will be collected at the same time point as the blood sample for clinical laboratory tests. Subjects will be instructed to take the study drug immediately after PK blood samples are collected. The exact date and time of last dose prior to the scheduled PK visit as recorded on the subject diary, the exact time of PK blood draws, and the exact time of dose taken at the site at the PK visit will be recorded on the appropriate eCRF.

Please refer to Appendix E for instructions for the collection, handling, and shipping of plasma samples for PK analysis. Samples collected from subjects in the vortioxetine and paroxetine groups will be analyzed by the bioanalytical laboratory to measure vortioxetine and paroxetine concentrations in plasma, respectively. Samples collected from subjects in the placebo groups will not be analyzed. The bioanalytical laboratory will be unblinded to select the subjects receiving vortioxetine or paroxetine.

9.1.16.2 Bioanalytical Methods

Plasma concentrations of vortioxetine and paroxetine will be measured by a validated high-performance liquid chromatography with tandem mass spectrometry method.

9.1.17 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at the Screening Visit, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure. The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.

Did not meet inclusion criteria or did meet exclusion criteria (specify reason).

- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

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

9.1.18 Documentation of Rescreening

Rescreening of subjects who do not meet eligibility requirements is not allowed. If the principal investigator believes in the appropriateness of the subject for the study and considers a rescreen, permission for this must be obtained from the medical monitor. Rescreening at the investigator's discretion without prior approval from the medical monitor is not permitted.

9.1.19 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 Period.

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

9.2 Monitoring Subject Treatment Compliance

A digital compliance technology will be implemented in this study, as described below. Subjects will also be required to bring study drug containers to each clinic visit, regardless of whether the study drug container is empty.

Subjects will be monitored for compliance using AiCure's artificial intelligence platform. The technology will be provided as a smartphone application. Subjects will use the smartphone application to monitor themselves taking the study drug. Subjects will either download the application to their own smartphone, or for subjects who do not have a smartphone or who do not wish to download the application to their own device, a smartphone-like device will be issued to them and must be returned at the end of their participation in the study. The Health Insurance Portability and Accountability Act (HIPAA)–compliant artificial intelligence software is able to identify and confirm the subject, the study drug, and ingestion of the study drug.

The subjects will monitor themselves taking the study drug using the application each time they take the study drug during the study. At the required dosing time, the software provides a reminder and takes the subject through a multistep process: (1) subject identification; (2) study drug identification; (3) confirmation that the subject has placed the study drug in his or her mouth. After determination of medication adherence by the smartphone application, data captured will be encrypted and transmitted to a secure, centralized, web-based dashboard, which the study site can access through a roles-and-rules-restricted, HIPAA-compliant system. When a subject is initially registered, a residential and/or mobile phone number will be encrypted and stored onto the dashboard. Subjects will also be able to manually enter into their device at a later time period if they took study drug but did not have their device on them, or if it was not working at the time.

If the study drug is not taken or is not taken correctly, the study site will be notified through the dashboard as well as by email or short message service (SMS) messaging. Study sites will be able to intervene with the subject directly through the dashboard if the study drug is not taken or not taken correctly. In addition, subjects will receive an automated message to their device reminding them to take their study drug, or if there is a low battery. The device will ring if subjects are late in taking their study drug. Subjects will provide written consent to be contacted via SMS messaging

in accordance with their use of the AiCure platform, at the clinical site when agreeing to participate in the study.

Subjects will be trained on how to use the application and will participate in a practice session at the Baseline Visit. During the practice session, subjects will be requested to take small practice pills to demonstrate that they are able to use the application. The practice pills are a commercially available product (ie, small white or colored candies) and will be provided by AiCure.

If a subject is persistently noncompliant with the study drug (eg, ≥4 consecutive doses missed and/or <70% compliant between visits), the medical monitor should be consulted to discuss whether it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

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

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

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.15. The genetic material will be preserved and initially stored at PPD Central Laboratory and then at PPD for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

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

Subjects who consented and provided PGx blood samples for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time. The sponsor should be notified of any withdrawal of consent. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study 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.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) 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 findings:

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

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

- If abnormal laboratory values 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, 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 appropriately 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 efficacy):

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

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.

Suicidality events:

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

10.1.4 SAEs

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

1. Results in DEATH.
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
	Acute liver failure
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
TEN/SJS	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

SJS=Stevens-Johnson syndrome, TEN=Toxic epidermal necrolysis.

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

10.1.5 Special Interest Adverse Events

A special interest AE (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 and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

10.1.5.1 Skin and Allergic Type Reactions

Any subject who develops rash should undergo assessment to characterize the nature and location of the rash. Subjects should be adequately examined for any clinical features that might suggest a developing drug reaction with eosinophilia and systemic symptoms (DRESS), a developing TEN,

or 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 tests should also be performed and the results 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, the Skin- or Allergy-Type Reaction page of the eCRF should be completed within 1 business day of the investigator's awareness of the event. If the alternative causality has been identified, then the Skin- or Allergy-Type Reaction page of the eCRF should not be completed.

10.1.5.2 Liver Injury

Management of liver toxicity AEs is described in Section 7.4. 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 of the eCRF. The investigator must contact the medical monitor for consideration of immediate discontinuation of study drug and discussion of relevant subject details and possible alternative causalities.

For events that meet the criteria described in Section 7.4, the Liver Injury page of the eCRF should be completed within 1 business day of the investigator's awareness of the event.

10.1.5.3 Overdose

Management of an overdose is described in Section 8.1.4. All cases of overdose (with or without associated AEs) will be documented as AEs. For events that meet the criteria of an overdose, the Overdose page of the eCRF 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 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/PTEs (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, or dosing with study drug was already stopped before the onset of the AE.

10.1.13 Outcome

- Recovered/Resolved – the 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; or 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; the event 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 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

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 (on Day 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 (on Day 1). Routine collection of AEs will continue until the Follow-up Contact (Week 7).

10.2.1.1 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 and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug (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.

The CSFQ-14, PGI-I scale, and C-SSRS 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 these instruments, 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.

10.2.1.2 Special Interest Adverse Event Reporting

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

10.2.2 Collection and Reporting of SAEs

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

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject ID 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, the LFT Increases page of the 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, other acute liver disease, or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.12 must also be performed. In addition, the LFT Increases page of the 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 hospital notes (eg, ECGs, laboratory test results, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs, as applicable. 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 an 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 their IRB.

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 Case Report Forms (Electronic)

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. The eCRFs must be completed in English.

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

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

After 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 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 copies of eCRFs, including the audit trail, and detailed records of drug disposition to

enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (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 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 unblinding of subject treatment assignments. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

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

13.1.1 Analysis Sets

The full analysis set (FAS) will include all subjects who were randomized, received at least 1 dose of double-blind study drug, and have at least 1 valid postbaseline value for assessment of the primary efficacy endpoint. In FAS efficacy summaries, subjects will be analyzed by the treatment to which they were randomized.

To adjust for treatment noncompliance, one or more modified FAS populations will be defined.

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

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline characteristics will be listed and summarized for demographics (sex, age, Hispanic ethnicity, race, and BMI), physical examinations (including assessment of menopausal status), and medical history (including psychiatric history).

Baseline values for efficacy and safety variables will be presented in the tables that summarize data per study visit; however, baseline efficacy data will also be presented separately for all subjects randomized.

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

13.1.3 Efficacy Analysis

13.1.3.1 Primary Analysis

Mean change from Baseline in the CSFQ-14 total score difference for vortioxetine vs paroxetine after 5 weeks of treatment will be the primary endpoint. The primary analysis will be based on analysis of covariance (ANCOVA) using the last observation carried forward (LOCF) technique, with treatment, center, and sex as fixed factors, and baseline CSFQ-14 total score as covariate. The comparisons will be between each vortioxetine dose (10 or 20 mg) and paroxetine, and both statistical tests will be 2-sided. The Holm-Bonferroni method will be used to adjust for multiplicity and control the familywise type I error rate at a significance level of 0.05. If the smaller of the 2 p-values is <0.025, significance is obtained for the associated vortioxetine dose and the other dose will then be evaluated at a 0.05 significance level. Although vortioxetine will be compared with paroxetine in the primary analysis, paroxetine will also be compared with placebo to validate the study.

13.1.3.2 Secondary Analyses

Change from Baseline in CSFQ-14 total score for vortioxetine vs paroxetine, paroxetine vs placebo, and vortioxetine vs placebo at each visit will also be analyzed using ANCOVA and LOCF, with treatment, center, and sex as fixed factors, and baseline CSFQ-14 total score as covariate. Similar analyses will also be performed for the male and female subgroups. Comparisons to placebo will be made at the significance level of 0.05 outside of multiplicity control.

The percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any visit (using LOCF) during the double-blind Treatment Period will be analyzed by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

Change from Baseline in CSFQ-14 subscales 5 dimensions and 3 phases of the sexual response cycle will be analyzed at all visits using ANCOVA and LOCF similar to the primary analysis.

13.1.3.3 Additional Analyses

The percentage of subjects meeting criteria for sexual dysfunction (ie, CSFQ-14 total score ≤47 for men and ≤41 for women) at any 2 consecutive visits (using LOCF) during the double-blind Treatment Period will be analyzed by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

Time to sexual dysfunction as assessed by the CSFQ-14 will be analyzed using a Cox model with an exact method to handle ties, with treatment and sex as factors.

CSFQ-14 shift from normal (ie, CSFQ-14 total score >47 for men and >41 for women) at Baseline to abnormal (ie, CSFQ-14 total score ≤47 for men and ≤41 for women), and CSFQ-14 negative responders (decrease from Baseline in CSFQ-14 total score ≥3) will be analyzed at all visits by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

PGI-I will be analyzed by study visit using ANCOVA and LOCF, with treatment, center, and sex as fixed factors.

C-SSRS will be summarized by study visit for each treatment group using descriptive statistics.

13.1.4 PK Analysis

Plasma concentrations of vortioxetine and paroxetine will be presented in the data listings.

A population PK analysis will only be conducted for vortioxetine and/or paroxetine if deemed necessary.

13.1.5 PGx Analysis

DNA samples may be used to analyze the mode of action of vortioxetine, and RNA samples may be used for subsequent pathway analysis. Also, since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development using stored samples.

13.1.6 Safety Analysis

AEs

AEs will be reported throughout the study. AEs will be summarized using the safety analysis set.

The definition of treatment-emergent AEs will be provided in the statistical analysis plan. AEs will be coded using MedDRA and will be summarized by system organ class and preferred term for the double-blind Treatment Period and the entire study.

AEs that were reported more than once by a subject during the double-blind Treatment Period will be counted only once for that subject at the maximum severity.

Clinical Evaluations

Absolute values and changes from Screening/Baseline for clinical laboratory tests, vital signs, and weight will be summarized for each treatment group using descriptive statistics. Clinical laboratory test and vital sign results that are outside the normal ranges and potentially clinically significant will be flagged and tabulated. Physical examination findings will also be summarized for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Approximately 352 male and female subjects will be randomized to 4 treatment arms.

Assuming an SD of 8.5 for the change from Baseline in CSFQ-14 total score, a total of 352 male and female subjects (88 subjects per arm) is sufficient to achieve ≥80% power to detect a difference of 4.0 for vortioxetine 20 mg vs paroxetine 20 mg or for vortioxetine 10 mg vs paroxetine 20 mg by a 2-sample t-test with a 0.025 2-sided significance level. Given the proposed Holm-Bonferroni method for multiplicity control, the power to achieve the significance for each vortioxetine dose is approximately 85%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or its 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, 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, 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 its designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or its 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 or where the study drug 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 the US regulatory agency, the FDA. If the study site is contacted for an inspection by the FDA, the sponsor should be notified immediately. The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 Institutional Review Board Approval

IRBs must be constituted according to the applicable state and federal requirements of each participating region. The sponsor or its designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB 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 its designee will supply relevant documents for submission to the respective IRB 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 for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or its designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB 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 notify the 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 notification, no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB 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 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 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 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.

The subject 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 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 at the time of consent and prior to the subject entering into the study. The subject 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 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.

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

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a subject ID 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 ID 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, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs 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. All publications and presentations must be prepared in accordance with this section and the study site agreement. 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 Period	Base-line	Double-Blind Treatment Period				Final Visit/ ET Visit (a)	Follow-up Contact (b)
Study Day/Week:	**Days -28 to -1**	**Day 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 7**
Visit Windows (Days Relative to Baseline [Day 0]):		**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Screening/Baseline Procedures								
Informed consent	X							
Subject registry database	X							
Demographics, medical and/or psychiatric history, medication history	X							
Height, BMI	X							
ECG	X							
HBsAg, HCV, HIV, free testosterone, TSH, free T4, HbA1c (c)	X							
Urine drug screen	X	X						
Concurrent medical and psychiatric conditions	X	X (d)						
Inclusion/exclusion criteria	X	X (d)						
Eligibility verification	X	X (e)						
Safety Assessments								
Physical examination, weight	X	X					X	
Vital signs	X	X		X			X	
Concomitant medications	X	X	X	X	X	X	X	X
Hematology, serum chemistry, urinalysis	X	X (f)					X (f)	
C-SSRS	X	X	X	X	X	X	X	
PTE assessment (g)	X	X						
AE assessments (h)			X	X	X	X	X	X
Pregnancy test (hCG) (i)	X	X	X	X	X	X	X	
Sexual Functioning Assessments								
CSFQ-14 (j)	X	X	X	X	X	X	X	
PGI-I (j)			X	X	X	X	X	
Other Blood Sampling								
PK sample collection (k)					X	X	X	
DNA PGx sample collection (l)		X						
RNA PGx sample collection (m)		X					X	
Clinical Supplies								
Contact IWRS for subject ID/ medication ID/subject status	X	X	X	X	X	X	X	

	Screening Period	Base-line	Double-Blind Treatment Period				Final Visit/ ET Visit (a)	Follow-up Contact (b)
Study Day/Week:	**Days -28 to -1**	**Day 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 7**
Study drug compliance technology		X	X	X	X	X	X	
Dispense study drug		X (n)	X	X	X	X		
Study drug return/accountability/ compliance			X	X	X	X	X	

(a) Final Visit procedures to be conducted for subjects who withdraw early, except for those who withdraw their consent and refuse further contact.
(b) The Follow-up Contact will be conducted by telephone.
(c) TSH to be measured at Screening to exclude subjects with clinically significant thyroid dysfunction (hyperthyroidism or hypothyroidism), which may impact sexual functioning. If TSH value is outside the normal range, free T4 will be measured.
(d) To be updated at Baseline.
(e) A prerandomization form must be approved by the PPD medical monitor prior to randomization.
(f) Blood samples for clinical laboratory tests to be collected under fasting conditions at Baseline and Week 5/ET.
(g) PTEs to be assessed from the date of Screening up to the first dose of study drug on Day 1.
(h) AEs to be assessed daily from the first dose of study drug on Day 1 until the Follow-up Contact at Week 7.
(i) Serum test at Screening and urine test at all other visits. For women of child-bearing potential only.
(j) The subject should complete the CSFQ-14 before the PGI-I.
(k)Six PK blood samples to be collected for each subject (2 samples at each time point at Weeks 3, 4, and 5/ET) for measurement of plasma vortioxetine or paroxetine concentrations. At Week 5/ET, the blood sample will be collected at the same time point as the blood sample for clinical laboratory tests. Subjects will be instructed to take the study drug immediately after collection of the PK blood sample.
(l) One 6-mL whole blood sample to be collected for DNA isolation predose at Baseline (Day 0) from each subject.
(m) Two 2.5-mL whole blood samples to be collected for RNA isolation predose at Baseline (Day 0) and also at Week 5/ET from each subject (ie, 4 samples per subject).
(n) Subjects are to be instructed to take the first dose of study drug on the morning of Day 1 (morning after Baseline).

Appendix B Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB 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 and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB. 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.
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.

Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

11. 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, and the monitor may inspect the records. By signing a written informed consent form, the subject 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 and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject 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 PGx 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;
    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 patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study and for 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study 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.

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 Collection, Storage, and Shipment of Pharmacokinetic Samples

Instructions for processing of plasma samples for pharmacokinetic analysis of vortioxetine and paroxetine

1. Collect 6-mL of venous blood into a chilled Becton-Dickinson Vacutainer containing K_2EDTA (for vortioxetine) or sodium heparin (for paroxetine).
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 relative centrifugal force (RCF) at approximately 4°C in a refrigerated centrifuge. Note: If using a collection device other than a Becton-Dickinson Vacutainer refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma for each analyte should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.2 mL needs to be obtained for each sample. Labeling may include protocol number Vortioxetine-4001, matrix (plasma), subject ID (XXXX-XXX), nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower. No more than 60 minutes should elapse between blood collection and freezing the plasma sample.
6. Keep samples frozen at approximately -20°C or lower until shipment to the central laboratory.

Shipping of plasma for vortioxetine or paroxetine quantification

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Biological samples (plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples. Samples may be shipped on other days with the permission of the sponsor.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into a self-sealing bag (eg, Ziploc) containing additional absorbent material.

5. Using a permanent marker, write the subject ID, study drug (vortioxetine or paroxetine), sample matrix (plasma), number of samples, and "SET 1" on each self-sealing bag.
6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2".
7. An inventory of individual samples should accompany each shipment and should include the sponsor's name (Takeda), protocol number (Vortioxetine-4001), investigator's name, sample type (plasma), subject ID, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2". Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the central laboratory.
8. For sample packing, use dry ice generously (eg, 20 to 25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a polystyrene (eg, Styrofoam) container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the polystyrene container. Place the lid on the polystyrene container and seal completely with strapping tape. Place the polystyrene container in a cardboard shipping carton and seal securely with strapping tape.
10. Mark the outside of shipping carton(s) with a tally number (1 of 5, 2 of 5, etc).
11. Affix an address label to each shipping carton. Use the preprinted air waybills provided by the central laboratory.
12. Obtain the air waybill number and a receipt of shipment from the carrier.

Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarify inclusion and exclusion criteria.

The primary change occurs in Sections 7.1 Inclusion Criteria and 7.2 Exclusion Criteria:

Initial wording:	Inclusion criterion #4: The subject has been in a steady relationship for ≥3 months and plans to remain in that relationship for the duration of the study, and is currently sexually active (≥2 times per week). Inclusion criterion #6: If female, the subject has a regular menstrual cycle. Exclusion criterion #12: The subject has a history of depression or any other psychiatric illness. Exclusion criterion #15: The subject has had a surgical or medical procedure on reproductive/genitourinary organs (excluding uncomplicated vasectomy and tubal ligation). Exclusion criterion #21: The subject has a history of or current alcohol or other substance abuse or dependence.
Amended or new wording:	Inclusion criterion #4: The subject has been in a steady relationship for ≥3 months and plans to remain in that relationship for the duration of the study, and is currently sexually active (≥2 times per week). **Note: Partners are not allowed to enroll in this trial.** Inclusion criterion #6: If female, the subject has a regular menstrual cycle **(note: amenorrhea resulting from hormonal contraceptives is not exclusionary)**. Exclusion criterion #12: The subject has a history of depression or any other psychiatric illness **including sleep disorders and premenstrual dysphoric disorder**. Exclusion criterion #15: The subject has had a surgical or medical procedure on reproductive/genitourinary organs (excluding uncomplicated **cesarean section (C-section),** vasectomy, and tubal ligation **that do not impact sexual functioning**). Exclusion criterion #21: The subject has a history of or current alcohol or other substance abuse or dependence **(according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised [DSM-IV-TR] criteria)**.

Rationale for Change:

Inclusion and exclusion criteria were revised to provide further specificity in response to questions from investigators about eligibility.

The following section also contains this change:

- Section 2.0 STUDY SUMMARY.

Change 2: Update, correct, or clarify excluded medications and treatments.

The primary change occurs in Section 7.3 Excluded Medications and Treatments, Table 7.a Excluded Medications and Treatments:

Description of changes: Chronic use of NSAIDs is excluded *only after* Baseline, not excluded for 3 months prior to Baseline. Furthermore, episodic use is allowed: **up to 2 doses of ibuprofen or naproxen per week is allowed. Aspirin is NOT allowed**.

Added: **antineoplastics are disallowed for 3 months Prior to/From Baseline** (already disallowed during the study as either chronic or episodic use).

Melatonin and topical steroids are **not excluded** before or during the study.

Rationale for Change:

The short half life of NSAIDs does not require a 3-month washout period and occasional use of ibuprofen or naproxen will not affect sexual function. Aspirin continues to be disallowed as it is counterindicated with paroxetine. Due to potential length of washout, antineoplastics must be stopped at least 3 months prior to start of study. Use of melatonin and topical steroids are allowed as they are not expected to affect sexual function.

Change 3: Add that psychiatric history will be assessed as well as medical history.

The primary change occurs in Section 9.1.3 Demographics, Medical History, Psychiatric History, and Medication History Procedure:

Initial wording:	Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions.
Amended or new wording:	Medical **history 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 stopped at or prior to signing of informed consent. Ongoing **medical and/or psychiatric** conditions are considered concurrent ~~medical~~ conditions.

Rationale for Change: Change made to clearly outline that an assessment of psychiatric disorders is required as they are exclusionary and may have an effect on the study outcome.

The following sections also contain this change:

- Section 9.1.11 Documentation of Concurrent Medical and/or Psychiatric Conditions.
- Appendix A Schedule of Study Procedures.

Change 4: Add instructions on the order in which the scales Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) and Patient Global Impression of Improvement (PGI-I) should be completed.

The primary change occurs in Section 9.1.8.1 CSFQ-14:

Added text: **The subject should complete the CSFQ-14 scale before the PGI-I scale at all post-baseline visits.**

Rationale for Change: The PGI-I is a global assessment which is more appropriate to complete after the specific questionnaire on sexual functioning (CSFQ-14).

The following sections also contain this change:

- Section 9.1.8.2 PGI-I Scale
- Appendix A Schedule of Study Procedures, footnote (j).

Change 5: Update personnel changes.

The primary change occurs in Section 1.1 Contacts and Section 1.2 Approval:

Initial wording: Responsible Medical Office	PPD
Amended or new wording:	PPD

Initial wording: Signatures	PPD
Amended or new wording:	PPD

Rationale for Change: A new responsible medical monitor/signatory was installed.

A Randomized, Double-Blind, Parallel Group, Placebo- and Active-Controlled, Phase 4 Study Evaluating the Effect of Vortioxetine 10 and 20 mg/day vs Paroxetine 20 mg/day on Sexual Functioning in Healthy Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	11-Jan-2017 17:16 UTC
	Clinical VP Approval	11-Jan-2017 18:14 UTC
	Biostatistics Approval	12-Jan-2017 13:31 UTC