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

NCT Number: NCT02371980

SAP Approve Date: 12 June 2019

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- Named persons or organizations associated with the study.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Lu AA21004_402

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

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

PHASE 4

Version: Final

Date: 12 June 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 1

Protocol Date: 25 September 2015

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the plasma concentration-time curve from time 0 to the end of the dosing interval (τ)
BMI	body mass index
BUN	blood urea nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
Cavg	average plasma concentration at steady state
CGI	Clinical Global Impression Scale
CGI-I	Clinical Global Impression Scale-Global Improvement Scale
CGI-S	Clinical Global Impression Scale-Severity of Illness Scale
CI	confidence interval
C_{max}	maximum plasma concentration at steady state
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
HAM-A	Hamilton Anxiety Scale
HDL	high density lipoprotein
ICH	International Conference on Harmonization
IMP	investigational medical product
LDL	low density lipoprotein
LLN	lower limit of normal
LOCF	last observation carried forward
LS	least squares
MADRS	Montgomery Åsberg Depression Rating Scale
MAR	missing at random
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	nonlinear mixed effect modeling
OC	observed case
PCS	potentially clinically significant

PE	physical examination
PK	pharmacokinetic
PPS	per protocol set
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SI	Systeme International
SOC	system organ class
TEAE	treatment-emergent adverse event
TDC Americas	Takeda Development Center Americas, Inc.
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

3.0 OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objective

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

3.3 Safety Objective

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

3.4 Additional Objectives

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

3.5 Study Design

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

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

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

treatment period. During the open-label period all subjects will receive 10 mg vortioxetine. Subjects will take their first dose of study medication the morning after their Baseline I visit. During the open-label treatment period, subjects will be seen every 2 weeks until randomization (Baseline II).

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

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

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

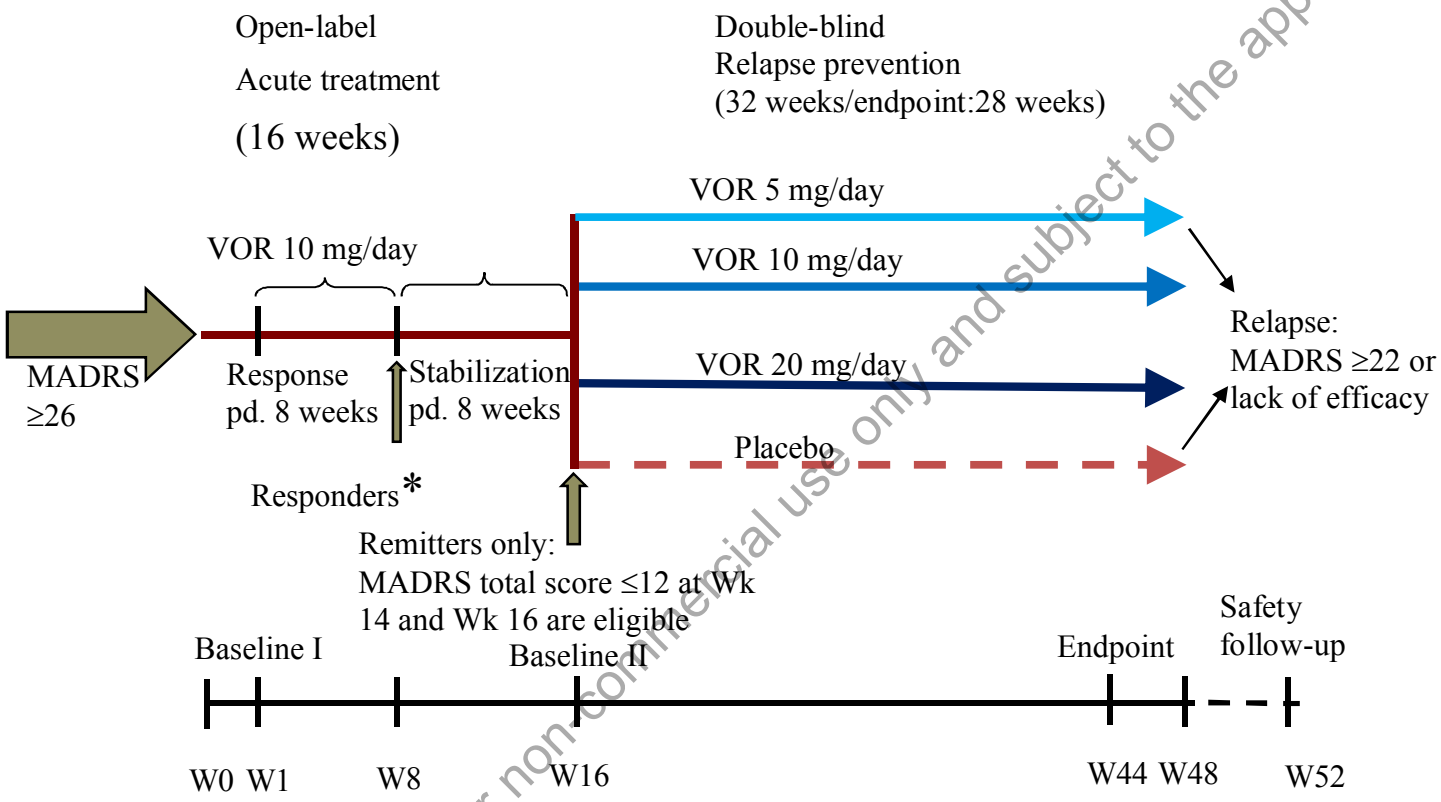
Subjects will be considered as "relapsed" and withdrawn from the study if the following criteria are met: MADRS ≥22, or lack of efficacy as determined by the investigator. In addition, investigator judgment should be used to determine unsatisfactory treatment response indicative of relapse to depression,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

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

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

A schematic of the study design is included as Figure 3.a. A schedule of assessments is listed in the protocol.

Figure 3.a Schematic of Study Design



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

VOR = vortioxetine, pd. = period

4.0 ANALYSIS ENDPOINTS

4.1 Primary Endpoint

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

4.2 Secondary Endpoints

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

4.3 Safety Assessments

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

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

4.4 Additional Endpoints

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

5.0 DETERMINATION OF SAMPLE SIZE

Assuming a cumulative relapse rate at 28 weeks of 15% for the vortioxetine group versus 30% for the placebo group, a total of 600 subjects (150 per treatment group) will provide 85% power to find a statistically significant difference between each dose of vortioxetine and placebo at a 5% significance level (ie, alpha=0.05). The total number of relapse events required in the placebo and three vortioxetine groups is about 110.

It is anticipated that approximately 55% of the patients enrolled into the open-label period will qualify for the double-blind study phase. Therefore, a total of about 1100 patients will need to be enrolled into the open-label period of the study.

If the number of subjects who relapsed during the double-blind treatment period is much less than expected, sample size adjustment will be considered. After approximately 75% of planned subjects (825) are enrolled into the open-label period of the study, the total number of relapse events, the numbers of subjects who have completed or are still in the double-blind treatment period, and the numbers of subjects in the open-label phase will be used to predict the final total number of relapse events. If the predicted total number of relapse events is far smaller than 110, with the planned 1100 enrolled subjects, more subjects will be enrolled in the study. All of these evaluations will be done while maintaining the study blind. The details for these analyses are in Appendix E.

As the number of randomized subjects, and ultimately the number of relapse subjects, are partly dependent on the number enrolled in the open-label period, the final number enrolled may be more than the estimated 1100.

6.0 METHODS OF ANALYSIS AND PRESENTATION

6.1 General Considerations

6.1.1 Statistical Software

Statistical analysis will be performed using the SAS System®, Version 9.4 or greater, on a Windows platform.

6.1.2 Summary Statistics and Precision

All tabulations of analysis results will include summaries for the following treatment groups: placebo, vortioxetine 5 mg QD, vortioxetine 10 mg QD, and vortioxetine 20 mg QD.

All confidence intervals, statistical tests, and resulting p-values will be reported as nominal 2-sided and will be assessed at the 5% significance level. No adjustments will be made for multiplicity aside from those for the primary efficacy analyses (see section 6.9.5).

For continuous variables, descriptive statistics will include the number of subjects (n), mean, SD or standard error (SE), as appropriate, minimum, median, and maximum. The number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the electronic case report form (eCRF) except for the CGI scales, where 2 decimal places will be reported.
- SD and SE: 2 more than the number of decimal places allotted in the eCRF.
- Minimum and maximum: equal to the number of decimal places allotted in the eCRF.
- Confidence intervals will be presented using the same number of decimal places as the parameters (eg, mean).

For categorical data, frequency counts and percentages will be presented. Percentages will be reported to 1 decimal place.

The data summaries will be accompanied by individual subject data listings sorted by treatment, study center and subject identifier. All data available from eCRFs will be listed. The actual day relative to the start of treatment will be determined and included in the listings.

Derived analysis datasets will be produced from raw data and laboratory data. This allows for convenient reviewing of the data as well as any necessary supplemental analyses. All data from the raw datasets will be included in the derived datasets. Derived dataset specifications will be developed to include the names and definitions of derived variables in the derived SAS datasets.

6.1.3 Definition of Study Day and Study Visit Windows

Visit windowing will not be used for the primary efficacy analysis and other time-to-event analyses in this study. For other analyses, a windowing convention will be used to determine the analysis value for a given study visit that applies to observed data.

In general, Study Day -1 corresponds to the date of the Baseline I or II visit. Other study days are defined relative to Study Day 1, the date of first study drug dose in the open label period or

double blind period. Relative day is calculated as (date of interest – date of first dose +1) for study days on or after the date of first dose and as (date of interest – date of first dose) for study days prior to the first dose date.

For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits. The visit windows and applicable study day ranges are presented below in Table 6.a and Table 6.b.

Table 6.a Visit Windows Open Label Period

Nominal Visit Week	Nominal Visit Day	MADRS, CGI-S, CGI-I, C-SSRS, Vital signs	Lab, Weight, PK	PE, Lipids fasted, ECG
Baseline I	-1 (a)	≤1 (b)	≤1 (b)	≤1
2	14	2 – 21		
4	28	22 – 35		
6	42	36 – 49		
8	56	50 – 63	2 – 94	
10	70	64 – 77		
12	84	78 – 91		
14	98	92 – 105		
16	112	≥106	≥95	≥2

(a) Baseline I day has been defined as Day -1 in keeping with Clinical Data Interchange Consortium standards. There is no Day 0.
(b) No baseline assessment for CGI-I or pharmacokinetic (PK) sampling. For others, last non-missing value prior to the first dose of study drug is defined as the Baseline.

Table 6.b Visit Windows Double-Blind Period

Nominal Visit Week	Nominal Visit Day	MADRS, CGI-S, C-SSRS, Vital signs	Weight	Lab, PE	ECG, PK	CGI-I
Baseline II/Week 16	-1 (a)	≤1	≤1	≤1	≤1	≤1
16+2=18	14	2 – 21	2 – 35	2 – 63		
16+4=20	28	22 – 42				
16+8=24	56	43 – 70	36 – 84			
16+12=28	84	71 – 98				
16+16=32	112	99 – 126	85 – 140	64 – 168	2 – 168	
16+20=36	140	127 – 154				
16+24=40	168	155 – 182	141 – 196			
16+28=44	196	183-210				
16+32=48	224	≥211	≥197	≥169	≥169	≥2

(a) Baseline II day has been defined as Day -1 in keeping with Clinical Data Interchange Consortium standards. There is no Day 0. The first dose in this table is the first dose in the double-blind study medication. Baseline value is the last non-missing observation prior to the first dose of the double-blind study medication.

More than 1 result for a parameter may be obtained in a visit window. In such an event, the result with the date closest to the scheduled visit day will be used. In the event of 2 observations equidistant to the scheduled visit day, the later of the observations will be used. Double-blind treatment Period Last Visit values will be defined irrespective of falling in a particular window. Hence, the windowed Week 48 value may be different than the Last Visit value.

In general, the baseline value, Baseline I or Baseline II, for a variable is defined as the last observation prior to the first dose of open-label or double-blind study medication (visit date ≤ first dose date) respectively, including the screening value, if necessary.

Adverse events that start more than 30 days after the last dose of study medication (start date – last dose date >30) will be listed, but excluded from the summaries and analyses. For efficacy and other safety data, data that are obtained more than 7 days after the last dose of study medication (visit date – last dose date >7) will be listed, but excluded from summaries and analyses.

If the date of the first open-label dose is missing, then the date of the first dose dispensed + 1 day will be used. If the date of the last open-label dose is missing and the subject is not randomized into double-blind period, then the earlier of the 2 dates will be used for the last open-label dose date for analysis and summary purpose: the early termination visit date or the last open-label drug dispense date +7 days. If the date of the last open-label dose is missing and the subject is randomized into double-blind period, then the date of first double-blind dose – 1 day will be used.

If the date of last double-blind dose is missing, then the earlier of the following 2 dates will be used for the last dose date for analysis and summary purpose: the final visit (Week 48) /early

termination visit date or the last double-blind drug dispense date +7 days. If the date of the first double-blind dose is missing, then the first dose dispensed date + 1 day will be used for analysis and summary purposes.

The study window convention will not be applied to the eCRF data listings. The data listings for eCRF data will display the raw data as collected and entered in the eCRF. For MADRS, CGI-I, and CGI-S, windowed visits will also be shown on the listings.

6.1.4 Grouping of Centers

Before unblinding the data, centers will be pooled with geographically similar centers to minimize artifacts in the statistical analyses from imbalances in subject counts within the centers.

The pooling of the centers will be reviewed and approved by the clinical team for agreement, and is then used in the appropriate analyses once the database is locked and unblinded.

6.2 Major Protocol Violations

All subjects with major protocol violations will be identified in the minutes of the subject evaluability assessment performed prior to unblinding, and will be listed by study center and subject number.

Subjects with the following major protocol violations will be excluded from the per protocol set (PPS) defined in Section 6.3:

- No evaluable baseline MADRS assessment.
- No evaluable post-baseline assessment of MADRS.
- Low study drug compliance (<70%) or missed study drug for 6 consecutive days.
- Double-blind study medication exposure less than 14 days (last dose date – first dose date +1 <14).
- Subjects switch treatment during study.

Other major protocol violations will be identified by the study team prior to unblinding.

6.3 Analysis Sets

The safety set for open-label period will include all subjects who received at least 1 dose of open-label study medication. The safety set for double-blind period will include all subjects who were randomized and received at least 1 dose of double-blind study medication. In safety summaries for the double-blind period, subjects will be analyzed according to the treatment they received. In the event that a subject inadvertently took capsules from more than 1 drug dose level, the actual treatment will be defined as the one taken most frequently. If the most common treatments were taken with equal frequency, the randomized treatment will be used as the actual treatment.

The full analysis set (FAS) will include all subjects who were randomized in the double-blind period and received at least 1 dose of double-blind study drug. FAS subjects with a non-missing baseline and at least one valid post-baseline value for an efficacy endpoint will be included in the

appropriate summaries and analyses. In FAS summaries, subjects will be analyzed by the treatment to which they were randomized.

The PPS will include all FAS subjects who had no major protocol violations. If more than 5% of the total subjects in the FAS have major protocol violations, analyses based on the PPS will be performed for the primary efficacy variable only.

The PK analysis set for open-label period will include all subjects who received at least 1 dose of open-label study medication and have at least 1 measurable open-label post-dose plasma concentration. The PK analysis set for double-blind period will include all subjects who received at least 1 dose of double-blind study medication and have at least 1 measurable double-blind post-dose plasma concentration.

6.4 Disposition of Subjects

Disposition for all enrolled subjects in the open-label period will be summarized. In addition, disposition for subjects who were randomized in the double blind treatment period will be summarized by treatment group and overall. The categories will include all subjects who were enrolled, subjects who were not treated, subjects who were randomized, subjects who discontinued from the study categorized by reason, subjects who discontinued treatment categorized by reason, and subjects who completed the study. The discontinuation reasons in the open-label period include pretreatment event or adverse event, significant protocol deviation, lost to follow-up, lack of efficacy, non-compliance with study drug, voluntary withdrawal, study termination, pregnancy, randomization criteria unmet, and other. The discontinuation reasons in the double-blind period include pretreatment event/adverse event, significant protocol deviation, lost to follow-up, lack of efficacy, relapse, non-compliance with study drug, voluntary withdrawal, study termination, pregnancy, randomization criteria unmet, and other. A listing will be presented to describe study period, treatment received during the period, date of first dose, date of last dose, date of completion or early withdrawal and the reason for early discontinuation. A summary of inclusion/exclusion criteria and responses for subjects with violations will also be provided.

6.5 Demographic and Baseline Characteristics

For subjects who were enrolled in the open-label period and took at least one dose of open-label drug, demographic and baseline I characteristics including gender, age, race, ethnicity, height, weight, body mass index (BMI), smoking habits, physical examination, and medical history including the number of prior episodes and the duration of current episode will be listed and summarized overall for Baseline I. For subjects who were randomized to the double-blind period, gender, age, race, ethnicity, height, weight, body mass index (BMI), smoking habits, physical examination, and medication history including the number of prior episodes and the duration of the current episode, will be summarized for Baseline II by treatment groups and overall based on double-blind safety set and the FAS, separately. Baseline I demographic and characteristics will also be summarizing for subjects who were enrolled in the open-label period but failed randomization.

Baseline values for efficacy parameters (MADRS and CGI-S) will be summarized in both open-label and double-blind treatment periods. CGI-I Baseline II values will be summarized in double-blind treatment period. Baseline I and Baseline II efficacy data will be presented for all enrolled subjects in open-label period and summarized by treatment group and overall based on all randomized subjects and the FAS, separately. Baseline I efficacy parameters will also be summarized for subjects who were enrolled in open-label period but failed randomization.

Height and weight values will be presented in metric units (cm and kg, respectively). BMI is calculated as [weight (kg)/height (m) ^{2}], using the weight collected prior to the first dose of the open-label or double-blind period.

Race is classified into Caucasian, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander. In addition, ethnicity (Hispanic or Latino) is also captured.

For continuous variables, the number of non-missing values and the mean, median, SD, minimum and maximum will be tabulated by treatment group and overall. For the categorical variables, the count and percentages of each possible value will be tabulated by treatment group and overall.

All individual demographic and baseline data will be listed by treatment, study center, and subject number.

6.6 Medical History and Concurrent Medical Conditions

Medical history refers to the significant conditions/diseases that stopped at or prior to Screening (time of informed consent). Concurrent medical conditions are those significant ongoing conditions/diseases present at Screening (time of informed consent).

For partially missing end dates, the following will be conducted:

- Day missing: the minimum between last day of the month and date of transfer will be used to impute the end date.
- Month and day missing: the minimum between last day of the year and date of transfer will be used to impute the end date.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or higher and will be summarized by treatment group and overall using system organ class (SOC) and preferred term (PT). The table will include number and percentages of subjects. SOC will be sorted in alphabetical order and the PT will be sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Summaries will be based on all enrolled subjects in open-label period and all randomized subjects in double-blind period. Concurrent medical conditions in the double-blind period include significant ongoing conditions or diseases present at the time of informed consent.

All medical history and concurrent medical condition data will be listed by treatment, study center and subject number. The listing will contain subject identifier, whether there was any

significant medical history or concurrent condition, including system organ class, preferred term and details of the medical history or condition.

6.7 Medication History and Concomitant Medications

The medication history and concomitant medications are defined as follows:

- Medication history refers to the medication that the study subjects stopped taking within 90 days prior to signing of informed consent.
- Concomitant medication is defined as medication that the study subjects continued taking or took from Screening through end of study:
  - Concomitant medication that started and stopped prior to baseline I (ie, stop date ≥ first screening visit date, and stop date ≤ first dose date).
  - Concomitant medication that started prior to Baseline I and was ongoing in the open-label period (ie, start date < first dose date, and stop date ≥ first dose date).
  - Concomitant medication that was ongoing in the double-blind period for the randomized patients (ie, start date ≤ last double-blind dose date, and stop date>first double-blind dose date).
  - Concomitant medication taken during the study (ie, start date ≤ last dose date, and stop date ≥first dose date.
  - If start date and stop date are missing, medication will be assumed to occur both prior and concomitantly.

For missing dates of concomitant medication, the following will be conducted:

- Missing start date:
  - Day missing: the first day of the month will be used for the start date.
  - Month and day missing: January 1 of that year will be used for the start date.
  - Year, month and day all missing: If date of birth is available, use the date of birth as the start date. If date of birth is not available, estimate date of birth using the screening date and age, and use the estimated date of birth as the start date.
- Missing end date:
  - Day missing: the last day of the month will be used for the end date. If the imputed end date is before the start date, keep the end date same as the start date.
  - Month and day missing: December 31 of that year will be used for the end date.
  - Year, month and day all missing: December 31 of the last dose year will be used for the end date. If the imputed end date is before the start date, keep the end date same as the start date.

Medication history and concomitant medications will be coded using the 01MAR2015E version of the World Health Organization (WHO) Drug Dictionary and summarized by giving the number and percentage of subjects by preferred term within each therapeutic class, with therapeutic class and medications in each class sorted in alphabetical order. The total number of

subjects with medications will also be summarized overall for open-label period, by treatment groups and overall for the double-blind period. If a subject reports taking 2 drugs belonging to the same class, he/she will only be counted once within that class. Summaries of medication history and concomitant medication will be based on all subjects in the open-label period and randomized subjects for the double-blind period.

All prior and concomitant medications will be listed by treatment, study center and subject number. The listings will contain subject identifier, WHO Drug preferred term and reported term, dose, unit, route, frequency, the indication for which the medication was being taken, start date, stop date, and whether the medication was ongoing.

6.8 Study Drug Exposure and Compliance

The summary of study drug exposure and compliance will be based on the safety set. Duration of exposure to study medication is defined as (date of last dose – date of first dose +1). Since study medication for the same subject in the open-label and double-blind periods may be different, the summary will be provided separately. Date of last dose is defined as the last dose in the treatment period.

Treatment duration will be summarized by duration category in days (open-label period: 1 to 13 days, 14 to 27 days, 28 to 41 days, 42 to 55 days, 56 to 69 days, 70 to 83 days, 84 to 97 days, 98 to 111 days, and ≥112 days; double-blind period: 1 to 13 days, 14 to 27 days, 28 to 55 days, 56 to 83 days, 84 to 111 days, 112 to 195 days, and ≥196 days) and the number of subjects in the double-blind duration category by treatment group. Treatment duration (weeks) will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Percent of study drug compliance is defined as {(number of capsules dispensed – number of capsules returned)/(date of last dose – date of first dose +1)}x100%. If a value for the number of returned capsules is missing or the return date is missing, then 100% compliance will be assigned for each day up to the number of capsules dispensed or up to the date of return whichever is earlier.

For each treatment group, study medication compliance will be summarized by compliance category (<80%, 80 to 120%, and ≥120%) and the number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment group.

All study drug administration and accountability data will be listed by treatment, study site, and subject number. The following variables will be listed: subject identifier, visit number, first and last dose dates, medication identification number, date dispensed and returned, number of capsules dispensed and returned, and percent compliance.

6.9 Primary, Secondary and Additional Analyses

6.9.1 Overview of Primary, Secondary and Additional Variables

The analyses and summaries will be based on the FAS.

Relapse is defined as either:

- a MADRS total score of 22 or more or
- lack of efficacy as determined by the investigator
- other unsatisfactory treatment response judged by the investigator.

The 'Time to Relapse' is in general defined as:

Date of Relapse – Date of Randomization (Visit 10) + 1

The date of relapse will normally be equal to the date of study drug discontinuation in the double-blind treatment period. If the date of study drug discontinuation is missing, date of last contact from study visit discontinuation will be used.

The time to relapse will be analysed using two different conventions:

Relapse Convention 1: Within 28 Weeks (primary):

This convention essentially only considers data during the first 28 weeks of the 32-week double-blind treatment, i.e., data up to week 44.

All withdrawals (relapses or other reasons) occurring after Visit 18/Week 44 will be regarded as censored observations and will be assigned the date of Visit 18 as censoring time.

Patients who did not relapse and withdrew before or at Visit 18 will be considered as non-relapse and will receive the date of study drug withdrawal as censoring time. If the date of study drug withdrawal is missing, the date of last contact will be used as censoring time.

The variables associated with these conventions will be defined as below,

Status_1: "0" indicating "Censoring"; "1" indicating "Relapse"

T_Relapse_1: Time to Censoring or Relapse.

These variables will be the basis for the primary analysis of efficacy.

Relapse Convention 2: Complete double-blind period (Secondary):

All relapses occurring in the entire 32-week double-blind period will be considered. All withdrawals who did not relapse will be considered as non-relapse and will receive the date of study drug withdrawal as censoring time. If the date of study drug withdrawal is missing, the date of last contact will be used as censoring time.

The variables associated with these conventions will be defined as below,

Status_2: "0" indicating "Censoring"; "1" indicating "Relapse"

T_Relapse_2: Time to Censoring or Relapse.

These variables will be the basis for secondary analysis of efficacy.

The primary, secondary and additional variables for this study are presented in Table 6.c.

Table 6.c Primary, Secondary and Additional Variables

Parameter	Description	Variable Type (a)
T_Relapse_1	Time to Relapse within 28 Weeks	4
T_Relapse_2	Time to Relapse within 32 Weeks	4
MADRS	MADRS total score	1
CGI-S	CGI severity	2
CGI-I	CGI improvement	2
T_withdrawal	Time to withdrawal for any reason within 28 Weeks	4
C-SSRS	C-SSRS response	2

(a) 1 = continuous; 2 = categorical; 3 = binary; 4 = time to event.

6.9.2 Missing Items on Rating Scales

The general rule when individual items are missing from a multiple-item assessment is as follows: the total score will be calculated using a SAS function CEIL, as CEIL[(sum of nonmissing items)×(total number of items)/(number of nonmissing items)]. If more than 20% of the items are missing, the total score will be set to missing. The MADRS total score will be set to missing if the number of missing items is at least 3. The resulting calculated total scores will be used in all analyses.

6.9.3 Analysis of Primary Variable

The time from randomization to relapse during the first 28 weeks of the 32-week double-blind treatment will be the primary variable. Primary analysis will compare the efficacy of vortioxetine (5, 10, and 20 mg) versus placebo based on a Cox proportional hazards model using an exact method to handle ties, with treatment as the factor and baseline MADRS total score as the covariate of the Cox model.

The SAS code for the time-to-relapse analysis will be as follows:

proc phreg;

- class treat;
- model T_Relapse_1*status_1(0) = treat baseline/ ties=exact;

Here, baseline is the MADRS score at the double-blind baseline (Baseline II). The analysis will be supplemented with plots of Kaplan-Meier estimates of relapse. The tests will be 2-sided comparing each of the 3 doses of vortioxetine to placebo. Ninety-five percent confidence intervals will be presented together with the estimated p-values.

In order to support the results of the primary analyses, a number of sensitivity analyses will be performed including the one described in the secondary analyses. In addition, since covariate adjustment in the Cox regression model requires stronger model assumptions, the covariate baseline MADRS total score will be excluded and only the treatment factor will be kept as the independent variable in the Cox model of the primary analysis. The standard log-rank test and

the accelerated failure time models will be also performed. Various distribution will be studied in the parametric models e.g. Weibull, log-normal and log-logistic. Sensitivity analyses, using the same methodology as for the primary analysis, will be performed where patients with relapses occurring within the first 14 days of the double-blind period are excluded (considered to have rebound instead of relapse) and where AE withdrawal is counted as relapse event, respectively. The primary analyses (Cox model) will be also be repeated based on the PPS.

Some covariates including pooled center, race, Baseline I and II MADRS scores, sex, baseline weight, BMI, and age with interaction terms may also be added to the Cox model of the primary efficacy analysis for exploratory analyses.

For the primary efficacy variable, subgroup analyses by:

- age (≤median, >median).
- sex (female, male).
- race (white, non-white).
- Baseline II MADRS (≤ median, > median).

and other variables, if necessary, will be performed if each of the subgroups contains at least 20% of the total subjects in the study. The treatment groups will be compared within each subgroup. Additional exploratory analyses examining subgroup effect and treatment by subgroup interaction may be performed.

6.9.4 Analysis of Secondary Variables

Change from double-blind Baseline II in MADRS total score will be analyzed using a mixed effects model for repeated measurements (MMRM) analysis with treatment, week, baseline MADRS total score, treatment-by-week interaction as fixed effects, center as random effect, and a completely unstructured covariance matrix**.** Study visits with at least 50% of the subjects have non-missing values will be included. Comparisons between the different doses of vortioxetine and placebo will be performed over all the assessment points.

The SAS code for the MMRM analysis will be as follows:

Proc mixed data=all;
- class week treat center subject;
- model Change = treat center week baseline week*treat /solution;
- repeated week/subject=subject type=UN;
- random center;
- lsmeans week*treat / cl pdiff.

Here, baseline is the MADRS score at baseline II, change is the change in MADRS score from baseline II, and week is to be recounted from baseline II.

Change from Baseline II in the CGI-S will be analyzed by study visit (including all visits for which at least 50% of the subjects have non-missing values) using MMRM similar to the model

described above for the change of MADRS total score. It should also be noted that the above longitudinal analyses (MMRM) on MADRS score change and CGI-S may be biased due to the unknown dropout pattern among the treatment groups.

Observed CGI-I scores will be summarized by treatment group for each visit.

Time from randomization to relapse of MDD occurring during the entire 32-week double-blind treatment period will be analyzed using a Cox model similar to the one described in 6.9.2 for the primary variable. It may also be considered a sensitivity analysis of the primary variable.

All statistical tests will be 2-sided and at the 5% level of significance. Ninety-five percent confidence intervals will be presented together with the estimated p-values.

6.9.5 Analysis of Additional Variables

The time from randomization to withdrawal for any reason during 28 weeks of double-blind treatment, will be analyzed using a Cox model similar to the one described in 6.9.2 for the primary variable.

The following summaries will be presented for C-SSRS scale:

- Descriptive statistics by study visit.
- Number of subjects with positive reports at baseline and during treatment.
- A shift-table to demonstrate changes in C-SSRS scores from baseline during treatment.

A subject with a positive report at baseline if the subject reported any of the following suicidal ideation or behavior:

- Active suicidal ideation with some intent to act, without specific plan.
- Active suicidal ideation with specific plan and intent.
- Any actual suicide attempt.
- Any interrupted suicide attempt.
- Any aborted suicide attempt.
- Any preparatory acts or behavior.

A subject with a positive report during treatment if the subject reported any of the following suicidal ideation or behavior:

- Active suicidal ideation with some intent to act, without specific plan.
- Active suicidal ideation with specific plan and intent.
- Any actual suicide attempt.
- Any interrupted suicide attempt.
- Any aborted suicide attempt.
- Any preparatory acts or behavior.
- Completed suicide.

6.9.6 Controlling Type I Error

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

6.10 Pharmacokinetic Analysis

The plasma concentration will be listed for each subject and summarized by each time point for each treatment group in both open-label and double-blind period (N, mean, SD, median, minimum, and maximum).

The population pharmacokinetics of vortioxetine and its metabolites will be assessed by means of nonlinear mixed effect modeling (NONMEM). Individual exposure parameters (eg, $AUC_{0-\tau}$, C_{avg}, C_{max}) maybe estimated and their correlation with relevant pharmacodynamic parameters may be explored (effect and tolerability/safety). A separate population pharmacokinetics plan and report will be written.

6.11 Pharmacogenomic Analyses

No pharmacogenomic analyses will be performed.

6.12 Safety Analysis

The safety data will be summarized for the open-label period and double-blind period separately. Safety summaries will be based on the safety set. Conventions for the definition of baseline values and visit windowing are given in Section 6.1.3. Missing safety data will not be imputed. Safety summaries will include descriptive statistics for values, changes, and incidence of events for all treatment groups combined in addition to summary by treatment group.

For adverse events with completely or partially missing date, the following will be conducted:

- Missing AE start dates:
  - Day missing:
    - If the month and year are the same as those in the first dose date, the first dose date will be used to impute the start date.
    - If the month and year are after the first dose date, the first of the month will be used to impute the start date.
  - Month and day missing:
    - If the year is the same as the year of the first dose, the first dose date will be used to impute the start date.
    - If the year is after the year of the first dose, set the start date as January 1.
  - Year, month, day all missing: the first dose date will be used to impute the start date.

- Missing AE stop dates:
  - Day missing: the last day of the month will be used to impute the end date. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.
  - Month and day missing: If the year is the same as or before the year of the last dose, set the end date as December 31. If the year is after the year of the last dose, set the end date as January 1.
  - Year, month, day all missing: Impute the end date as December 31 of the last dose year. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.

6.12.1 Adverse Events

All adverse events will be coded using MedDRA version 18.0 or higher. In this dictionary, each verbatim term is coded to a lower level term, and then mapped to a preferred MedDRA term, which is then mapped to an SOC. All adverse events will be included in the data listings, but only treatment-emergent adverse events will be included in the summary tables.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug (AE start date ≥ first dose date) and within 30 days after receiving the last dose of study drug (AE start date – last dose date ≤30). The first dose date and last dose date for the open label period and double blind period may be defined differently based on the summary table in the two treatment periods. A TEAE may also be a pretreatment adverse event or a concurrent medical condition diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing. Adverse events data with onset occurring more than 30 days after last dose of study drug (AE start date – last dose date >30) will be listed, but not included in the summary tables. Adverse events with missing onset dates will be summarized regardless of severity and relationship to study medication.

Serious adverse events (SAEs) with onset that occurs after receiving study drug (AE start date ≥ first dose date) and within 30 days after receiving the last dose of study drug (AE start date - last dose date ≤30) will be summarized.

In the high-level adverse event summary tables, TEAEs will be summarized regardless of intensity and relationship to study drug. Within each subject, multiple reports of events that map to a common MedDRA term will be counted only once.

At the adverse event level, the summary tables will present the number of subjects reporting each of these MedDRA events, ie, the number of subjects reporting 1 or more events that map to the given MedDRA term.

At the SOC level, the summary tables will present the number of subjects reporting 1 or more events that map to the given SOC. That is, the number of subjects reported at the SOC level will be less than or equal to the sum of the subject counts across all adverse events within that SOC.

In selected summaries (TEAEs overview, and TEAEs by SOC and preferred term), adverse events will be summarized by the number of events reported in addition to the number and percentage of subjects with events.

For the summary of TEAEs by SOC, preferred term and maximum intensity, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once within period by the maximum intensity of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the maximum intensity in that SOC. Adverse events with missing severity will be classified as having the highest severity.

TEAEs classified in the eCRF as possibly or probably related to the study medication will also be summarized by preferred term and SOC. If a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the most related report for the preferred term. Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the most related report in that SOC. Adverse events with missing relationship will be classified as having the highest relationship to study drug.

The following summaries will be presented separately for the open-label period and double-blind period:

- Overview of TEAEs during the study - number and percentage of subjects, number of events.
- TEAEs by SOC and preferred term - number and percentage of subjects, number of events.
- TEAEs by SOC and preferred term by sex (male and female) - number and percentage of subjects, number of events.
- TEAEs by SOC and preferred term by age group (≤median, >median) - number and percentage of subjects, number of events.
- TEAEs by SOC - number and percentage of subjects.
- TEAEs by preferred term - number and percentage of subjects.
- Most frequent (at least 5% in any treatment group) TEAEs by preferred term - number and percentage of subjects.
- Most frequent (at least 5% in any treatment group) non-serious TEAEs by preferred term - number and percentage of subjects.
- Intensity of TEAEs by SOC and preferred term - number and percentage of subjects.
- Drug-related TEAEs by SOC and preferred term - number and percentage of subjects, number of events.
- TEAEs leading to study discontinuation by SOC and preferred term - number and percentage of subjects, number of events.
- Treatment-emergent SAEs by SOC and preferred term - number and percentage of subjects, number of events.

SOCs will be sorted by alphabetical order. Within an SOC, adverse events will be sorted in descending order of total number of subjects with the preferred term among all the treatment groups.

For treatment emergent nausea, the following summaries will be presented additionally for open-label period and double-blind period:

- Duration of nausea during study.
- Time to first nausea.

Figures for point prevalence of nausea (occurring during the double-blind period – core phase) relative to number of subjects at risk for female, male, and overall will be presented.

All adverse events will be listed by treatment, study center, subject number, and onset date of the adverse event. The listing will contain: subject identifier, age, sex, body weight, race, adverse event (preferred term and reported term), SOC, onset date, end date or whether the event was ongoing, duration, frequency, intensity (mild, moderate or severe), action taken concerning study drug (change in concomitant medication, change in IMP, or subject withdrawal), causality to study drug (not related, possibly related, or probably related), the outcome (recovered, recovering, not recovered, recovered with sequelae, or death), whether the adverse event was an SAE and whether the event was an adverse event of special interest (AESI).

Special listings for TEAEs leading to study discontinuation, SAEs, deaths, duration of nausea during the study, and AEs of special interest will also be presented.

6.12.2 Clinical Laboratory Evaluations

The following clinical laboratory parameters will be summarized:

- Serum chemistry including blood urea nitrogen (BUN), sodium, alkaline phosphatase, potassium, calcium, creatinine, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, creatine kinase, total protein and GGT
- Lipids including cholesterol total, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).
- Hematology including white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelets, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.
- Urinalysis including pH, protein, glucose, occult blood and specific gravity.

For each laboratory parameter, the following will be displayed for each scheduled time point (each visit and end of study).

- Summary statistics (n, mean, SD, median, minimum, and maximum) by treatment group and overall for the actual values and change from Baseline values.
- Shift tables for the change from Baseline to each post-baseline time point will be presented. For these tables each subject will be categorized as low, normal, or high for the baseline

value, and low, normal, or high for each post-Baseline time point, according to the central laboratory reference ranges. The number of subjects in each of the combinations of shifts will be presented.

Potentially clinically significant (PCS) laboratory values, as defined in Appendix B, will be summarized by treatment group and overall. The number and percentage of subjects with PCS values observed post-Baseline in each of the applicable laboratory parameters will be presented.

A listing of all laboratory data will be provided. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting PCS criteria. The listing will also include the age (at consent) and sex of the subject. Listings of PCS laboratory values will also be presented. Thyroid stimulating hormone, Free T_4 (c), γ-Glutamyl transferase, and direct bilirubin will not be summarized but will be listed.

When lab values are recorded in the form of "<x" or ">y", "x" will be used for "<x" and "y" will be used for ">y" in the summary tables. However, these values will be displayed as is when the individual subject data listings are presented.

Summaries and listings of laboratory data will be presented, as appropriate, in System International (SI) and conventional units.

6.12.3 Liver Function Tests

Liver function tests will be summarized by visit. Number and percentage of subjects who meet liver function test criteria will be summarized by treatment.

6.12.4 Vital Signs and Weight

Vital signs and weight at scheduled visits and their changes from Baseline will be summarized overall for the open-label period and summarized for each treatment group and overall using descriptive statistics by visit and end of study for the double blind period, separately. The number and percentage of subjects with at least one post-Baseline PCS vital sign value during the double-blind treatment period will be presented for each variable over all visits. A listing of PCS vital signs values will also be presented.

The criteria for identification of PCS vital signs values are given in Appendix C.

6.12.5 Physical Examinations

All physical examination findings will be listed by treatment, study center and subject number. The following variables will be listed: subject identifier, age, sex, study visit, visit date, whether there was any clinically significant findings.

6.12.6 12-Lead ECGs

ECG variables at scheduled visits and their changes from Baseline will be summarized for each treatment group and overall using descriptive statistics by study visit and end of study. A shift table for the investigator's ECG interpretation will provide the number of subjects in each of the appropriate categories (Normal, Abnormal but not clinically significant, or Abnormal and

clinically significant) at the scheduled visit relative to the Baseline status. The number and percentage of subjects with at least one post-Baseline PCS ECG value during the double-blind treatment period will be presented for each variable over all visits. A listing of PCS ECG values will also be presented.

The criteria for identification of PCS ECG values are given in Appendix D.

6.12.7 Pregnancy Test

For females, pregnancy test results will be listed by treatment, study center, and subject number.

6.13 Interim Analysis

A blinded summary of ongoing data will be conducted when approximately 75% of the planned subjects are enrolled. See Appendix E for details about these calculations that will be used to verify the numbers of subjects to be enrolled.

6.14 Changes in the Statistical Analysis Plan From the Protocol Analysis Plan

Analysis of covariance (ANCOVA) model (using LOCF and OC) for MADRS, CGI-S and CGI-I won't be performed.

Comparability of treatment groups using analysis of variance for continuous variables and using Cochran-Mantel-Haenszel test for discrete variables for demographics and baseline characteristics won't be performed.

7.0 REFERENCES

1. A Randomized, Double-Blind, Placebo-Controlled, Phase 4, Relapse Prevention Study Evaluating the Efficacy and Safety of Vortioxetine (5, 10 and 20 mg) in Adults With Major Depressive Disorder. Takeda Global Research & Development Centre Inc., Protocol No. Lu AA21004_402 Incorporating Amendment No.1, dated 25 September 2015.

Appendix A Schedule of Study Procedures

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

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

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

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

Appendix A Schedule of Study Procedures (continued)

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

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

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

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

Appendix B Criteria for Identification of Potentially Clinically Significant Laboratory Values

Parameter	Unit Type	Unit (a)	PCS Definition
Hematology			
Hemoglobin	SI	g/L	Low: ≤0.9×LLN
	conventional	g/dL	Low: ≤0.9×LLN
Erythrocytes (red cell count [RBC])	SI	10^12/L	High: ≥1.1×ULN, Low: ≤0.9×LLN
	conventional	10^12/L	High: ≥1.1×ULN, Low: ≤0.9×LLN
Hematocrit (packed cell volume)	SI	Fraction of 1.00	Low: ≤0.9×LLN
	conventional	%	Low: ≤0.9×LLN
Total leucocytes (white cell count [WBC])	SI	10^9/L	High: ≥16, Low: ≤2.8
	conventional	10^9/L	High: ≥16, Low: ≤2.8
Neutrophils	SI	10^9/L	High: ≥15, Low: ≤1.4
	conventional	10^9/L	High: ≥15, Low: ≤1.4
Lymphocytes	SI	10^9/L	High: ≥7.0, Low: ≤0.6
	conventional	10^9/L	High: ≥7.0, Low: ≤0.6
Monocytes	SI	10^9/L	High: ≥2.5
	conventional	10^9/L	High: ≥2.5
Eosinophils	SI	10^9/L	High: ≥0.6
	conventional	10^9/L	High: ≥0.6
Basophils	SI	10^9/L	High: ≥0.6
	conventional	10^9/L	High: ≥0.6
Thrombocytes (platelet count)	SI	10^9/L	High: ≥700, Low: ≤75
	conventional	10^9/L	High: ≥700, Low: ≤75
Blood Chemistry			
Total bilirubin	SI	µmol/L	High: ≥34.2
	conventional	mg/dL	High: ≥2.0
Alkaline phosphatase	both	U/L	High: ≥3×ULN
Aspartate aminotransferase (AST)	both	U/L	High: ≥3×ULN
Alanine aminotransferase (ALT)	both	U/L	High: ≥3×ULN
Albumin	SI	g/L	Low: ≤25
	conventional	g/dL	Low: ≤2.5

Appendix B Criteria for Identification of Potentially Clinically Significant Laboratory Values (continued)

Parameter	Unit Type	Unit (a)	PCS Definition
Sodium	SI	mmol/L	High: ≥155, Low: ≤125
	conventional	mEq/L	High: ≥155, Low: ≤125
Potassium	SI	mmol/L	High: ≥5.5, Low: ≤3.0
	conventional	mEq/L	High: ≥5.5, Low: ≤3.0
Calcium (total)	SI	mmol/L	High: ≥3.0, Low: ≤1.75
	conventional	mg/dL	High: ≥12.0, Low: ≤7.0
Creatinine	SI	μmol/L	High: ≥175
	conventional	mg/dL	High: ≥2.0
Creatine phosphokinase (CPK)	both	U/L	High: ≥2×ULN
Glucose (non-fasting)	SI	mmol/L	High: ≥13.9, Low: ≤2.8
	conventional	mg/dL	High: ≥250, Low: ≤50
Cholesterol (total)	SI	mmol/L	High: ≥7.8
	conventional	mg/dL	High: ≥302
Triglycerides	SI	mmol/L	High: ≥3.40
	conventional	mg/dL	High: ≥301
High density lipoproteins (HDL) cholesterol	SI	mmol/L	Low: <0.9
	conventional	mg/dL	Low: <35
Low density lipoproteins (LDL) cholesterol	SI	mmol/L	High: ≥5.0
	conventional	mg/dL	High: ≥193
Total protein	SI	g/L	High: >1.2×ULN, Low: <0.8×LLN
	conventional	g/dL	High: >1.2×ULN, Low: <0.8×LLN
Blood Urea Nitrogen	SI	mmol/L	High: >10.7
	conventional	mg/dL	High: >30
γ-Glutamyl Transferase	both	U/L	High: >3×ULN
Urinalysis			
Glucose			N/A
Protein			N/A
Occult Blood			N/A
Pregnancy			N/A

(a) Systeme International (SI) units, conventional units and conversion factors were obtained from Laposata, Michael. SI Unit Conversion Guide. Boston: NEJM Books, 1992.
LLN=lower limit of normal range; N/A=not applicable; PCS=potentially clinically significant; ULN=upper limit of normal range.

Appendix C Criteria for Identification of Potentially Clinically Significant Vital Signs

Parameter	Unit	PCS Definition (a)
Systolic BP	mmHg	≥180 mmHg and an increase of ≥20 mmHg or ≤90 mmHg and a decrease of ≥20 mmHg
Diastolic BP	mmHg	≥105 mmHg and an increase of ≥15 mmHg or ≤50 mmHg and a decrease of ≥15 mmHg
Pulse	bpm	≥120 bpm and an increase of ≥15 bpm or ≤50 bpm and a decrease of ≥15 bpm
Body Temperature	°C	Low: <35.6
		High: >37.7
	°F	Low: <96.1
		High: >99.9
Weight	kg	Change of ≥7% body weight

BP=Blood pressure.
(a) PCS criteria are applied to postbaseline values and changes relative to Baseline values, as appropriate.

Appendix D Criteria for Identification of Potentially Clinically Significant 12-Lead ECG Parameters

Parameter	Unit	PCS Definition (a)
Heart rate	beats per minute	(≤50 bpm and Change ≤-15 bpm) or (≥120 bpm and Change ≥15 bpm)
RR	msec	(<500 msec and Change ≤-200 msec) or (>1200 msec and Change ≥200 msec)
PR	msec	<120 msec or ≥250 msec
QRS	msec	<40 msec or >150 msec
QT	msec	<280 msec or >500 msec
QTcB	msec	<340 msec or >500 msec or Change <-60 msec or Change >60 msec
QTcF	msec	<340 msec or >500 msec or Change <-60 msec or Change >60 msec

(a) PCS criteria are applied to postbaseline values and changes relative to Baseline values, as appropriate.

Appendix E Relapse Events Prediction for Possible Sample Size Adjustment

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	14-Jun-2019 16:49 UTC