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

SAP Approve Date: 24 July 2017

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

STUDY NUMBER: Vortioxetine-4001

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

PHASE 4

TAKEDA DEVELOPMENT CENTER AMERICAS, INC

Version**:** Final

Date**:** 24 July 2017

1.1 Approval Signatures

Study Title: 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

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27 July, 2017
Date

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27 July 2017
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2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CPK	creatine phosphokinase
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
CRF	case report form
ECG	electrocardiogram
FAS	full analysis set
GGT	γ-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PGI-I	Patient Global Impression of Improvement
PGx	pharmacogenomic
PK	pharmacokinetics
QOL	quality-of-life
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SDB	standard database
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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.

4.2 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.

4.3 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.

4.4 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 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,

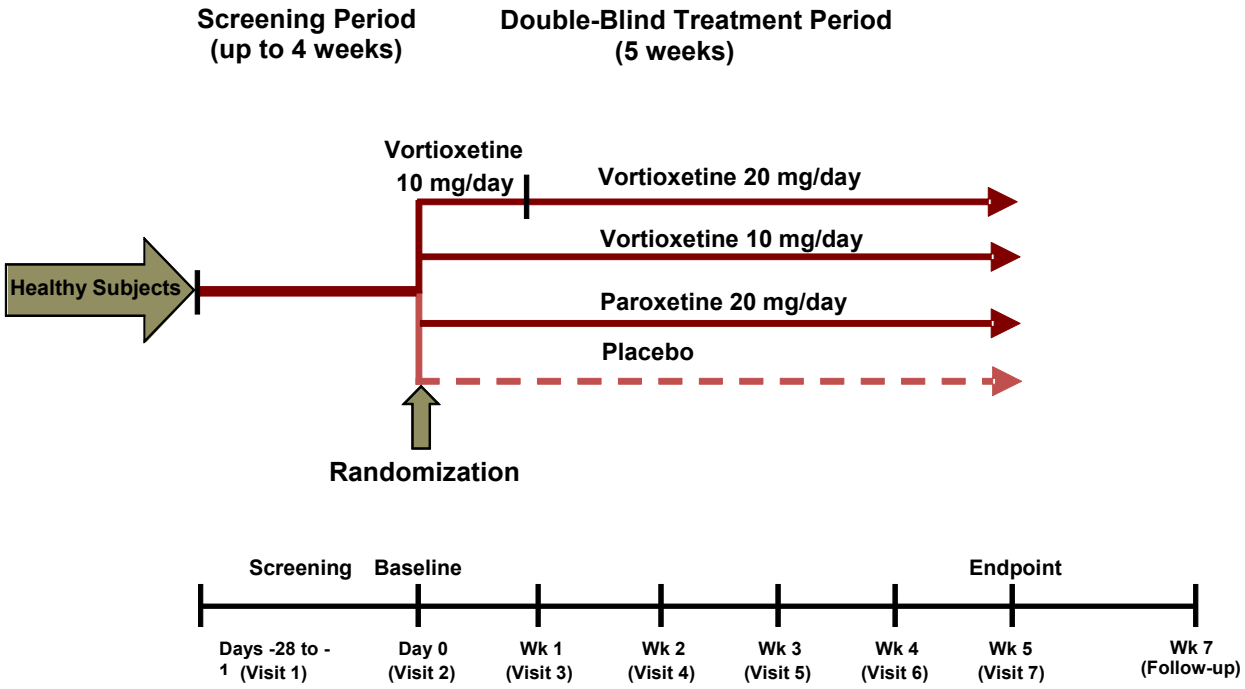
vortioxetine 20 mg, paroxetine 20 mg, or placebo and will be treated for 5 weeks. Randomization will be stratified by sex. Subjects allocated to vortioxetine 20 mg will initiate treatment at 10 mg/day for the first week. Subsequently, the dose will be increased to 20 mg/day and remain at 20 mg/day until 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, 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 during the double-blind Treatment Period and at the Final Visit. 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.

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 4.a. A schedule of study procedures is provided in Appendix A.

Figure 4.a Schematic of Study Design



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

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

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

5.2 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.

5.3 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.

5.4 Safety Assessments

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

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 352 male and female subjects will be randomized to 4 treatment arms. Randomization will be stratified by sex. Men and women will be enrolled in approximately equal proportions (ie, 50% men and 50% women overall).

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 (see Section 7.9.3) for multiplicity control, the power to achieve the significance for each vortioxetine dose is approximately 85%.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

7.1.1 Statistical Software

Statistical analysis will be performed using the SAS System®, Version 9.2 or greater, on a Windows platform.

7.1.2 Summary Statistics and Precision

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

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 analysis.

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.

7.1.3 Definition of Study Day and Study Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit that applies to observed data.

Study Day -1 corresponds to the date of the Baseline visit, ie, the randomization date. Other study days are defined relative to Study Day 1, the date of first double-blind study drug dose. 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 7.a.

Table 7.a Visit Windows

Nominal Visit Week	Nominal Visit Day	CSFQ-14, PGI-I, C-SSRS	Vital signs	Lab, PE,Weight,	PK
Baseline	-1 (a)	≤1 (b)	≤1	≤1	≤1 (b)
1	7	2 – 10			
2	14	11 – 17	2-24		
3	21	18 – 24			2-24
4	28	25 – 31			25-31
5	35	≥32	≥25	≥2	≥32
7	49				

(a) Baseline 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 PGI-I or pharmacokinetic (PK) sampling.

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. Treatment Period Last Visit values will be defined irrespective of falling in a particular window. Hence, the windowed Week 8 value may be different than the Last Visit value.

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

Adverse events that start more than 30 days after the last dose of double-blind 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 double-blind study medication (visit date – last dose date >7) will be listed, but excluded from summaries and analyses. For certain safety measurements such as laboratory tests, summary statistics for the last visit will be presented, which will display values closest to the last dose of the double-blind medication within the cutoff day for that variable.

If the date of the first double-blind dose is missing due to the subject being lost to follow-up after being dispensed drug then the first dose dispensed date + 1 day will be used for analysis and summary purposes. Similarly, if the date of last double-blind dose is missing, then the date of the last double-blind drug dispense date + (the last number of doses dispensed – the last number of doses returned) - 1 will be used.

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 CSFQ-14 and PGI-I, windowed visits will be shown on the listings.

7.1.4 Grouping of Centers

Before unblinding the data, centers that are considered small (<8 subjects) 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.

7.2 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):

- No evaluable baseline CSFQ-14 assessment.
- No evaluable post-baseline assessment of CSFQ-14.
- Low study drug compliance (<70%) or missed study drug for 4 consecutive days.
- Double-blind study medication exposure less than 7 days (last dose date – first dose date +1 <7).
- Subjects switch treatment during study.

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

7.3 Analysis Sets

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

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

To adjust for treatment noncompliance, two modified FAS populations, mFAS1 and mFAS2, will be defined based on the PK data. The mFAS1 excludes subjects in the vortioxetine treatment

arm who had drug concentration below the limit of quantification at all study visits where PK is collected, while the mFAS2 excludes subjects in the vortioxetine treatment arm who had drug concentration below the limit of quantification at any study visit where PK is collected. 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.

7.4 Disposition of Subjects

A subject disposition summary presented by treatment group and overall will be provided. The categories will include all subjects who were not treated, subjects who discontinued from the study early categorized by reason, subjects who completed the study, subjects who discontinued treatment early categorized by reason, and subjects who completed treatment. Post-randomization discontinuation reasons include pretreatment event or adverse event, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy, non-compliance with study drug, and other. A listing will be presented to describe study treatment, date of first dose, date of last dose, date of completion or early withdrawal, and the reason for early discontinuation.

A summary of screening failures and listings of inclusion/exclusion criteria responses for subjects with violations will also be provided.

7.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, age, race, ethnicity, height, weight, body mass index (BMI), smoking habit, female reproductive status, menstruation condition, and sexual dysfunction status. The demographic and baseline characteristics summary will be based on all randomized subjects. Summaries based on the full analysis set will also be created.

Baseline values for efficacy parameters (CSFQ-14) will also be presented for each treatment group and overall based on all randomized subjects.

Height and weight values will be presented in metric units (cm and kg). BMI is calculated as [weight (kg)/height (m) ^{2}], using the weight collected at the first screening visit (Visit 1) in the study.

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.

Female reproductive status is classified into four categories: postmenopausal, surgically sterile, female of childbearing potential and NA/subject is male. Menstruation condition includes duration of menstruation and duration of menstrual cycle.

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.

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

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

7.6 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).

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 and will be summarized by treatment group and overall using System Organ Class (SOC) and MedDRA preferred term. The table will include number and percentages of subjects with system organ class terms sorted alphabetically and preferred terms sorted by 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 randomized subjects.

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.

7.7 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 at or within 90 days prior to the Screening Visit (ie, stop date <= first screening visit date).
- 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 (ie, stop date > first screening visit date, and stop date ≤ first dose date).
  - Concomitant medication that started prior to and was ongoing at baseline (ie, start date < first dose date, and stop date > first dose date).
  - Concomitant medication that started after baseline but before or at last dose (ie, start date ≥ first dose date, and start date ≤ last 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.

Medication history and concomitant medications will be coded using the 01MAR2016E version of the World Health Organization (WHO) Drug Dictionary and summarized by giving the number and percentage of subjects by preferred term, with preferred terms sorted by decreasing frequency based on the total number of subjects. If a subject reports taking 2 drugs belonging to the same preferred term, he/she will only be counted once within that preferred term. Summaries of medication history and concomitant medication will be based on all randomized subjects.

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.

7.8 Study Drug Exposure and Compliance

The summary of study drug exposure and compliance will be based on the safety set.

Duration of exposure to double-blind study medication is defined as (date of last dose – date of first dose +1).Treatment duration will be summarized by duration category in days (1 to 6 days, 7 to 13 days, 14 to 20 days, 21 to 27 days, 28 to 34 days, and ≥35 days) and the number of subjects in each 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.

7.9 Efficacy Analysis

The analyses and summaries will be based on the FAS.

7.9.1 Overview of Primary, Secondary and Additional Variables

The primary, secondary and additional variables for this study are presented in Table 7.

Table 7.b Primary, Secondary and Additional Variables

Parameter	Description	Variable Type (a)
CSFQ-14	CSFQ-14 total score	1
PGI-I	PGI improvement	2
Sexual dysfunction (abnormal) assessed by CSFQ-14	CSFQ-14 total score ≤47 for men or ≤41 for women	3
Time to sexual dysfunction	Time to CSFQ-14 total score ≤47 for men or ≤41 for women	4
C-SSRS	Columbia-Suicide Severity Rating Scale	2
$CSFQ_i$	CSFQ-14 single item i	2
CSFQ 5-dimensions: Pleasure	CSFQ-14 item 1	2
CSFQ 5-dimensions: Desire/Frequency	Sum of CSFQ-14 items 2 and 3	1
CSFQ 5-dimensions: Desire/Interest	Sum of CSFQ-14 items 4, 5, and 6	1
CSFQ 5-dimensions: Arousal/Erection	Sum of CSFQ-14 items 7, 8, and 9	1
CSFQ 5-dimensions: Orgasm/Ejaculation	Sum of CSFQ-14 items 11, 12, and 13	1
CSFQ 3-phases: Desire	Sum of CSFQ-14 items 2, 3, 4, 5, and 6	1
CSFQ 3-phases: Arousal	Sum of CSFQ-14 items 7, 8, and 9	1
CSFQ 3-phases: Orgasm/Completion	Sum of CSFQ-14 items 11, 12, and 13	1
ΔCSFQ ≤-3	CSFQ negative response (≥3 decrease from baseline)	3
Time to ΔCSFQ ≤-3	Time to CSFQ negative response	4

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

7.9.2 Missing Items on Rating Scales

Missing values for post-baseline assessments will be imputed by the last observed value immediately prior to the missing value carried forward (LOCF). This rule does not apply to individual items in a multiple-item assessment. LOCF is used after imputation, ie, LOCF values are not used for calculations of subscale/scale scores.

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 implications of this rule are indicated in Table 7.c for each rating scale. The resulting calculated total scores will be used in all analyses.

Table 7.c Number of Missing Items on Rating Scales Associated with a Missing Value

for Total Score

Parameter	Number of Missing Items
CSFQ-14	≥3
$CSFQ_i$ or CSFQ dimension or CSFQ 3-phases	≥1

7.9.3 Primary Efficacy Endpoint(s)

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 following example SAS code will be used for the ANCOVA analysis:

Proc mixed data=all;

- class treat center sex;
- model Change= Baseline treat center sex;
- lsmeans treat;

In the above model, Baseline is the baseline value and Change is the change from baseline value.

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. The primary analyses will also be repeated based on the PPS if more than 5% of the total subjects in the FAS have major protocol violations.

As supportive analyses, the sex-by-treatment interaction term will be added to the primary analysis model to further check the sex effect on the treatment. The similar ANCOVA analyses will also be performed using the observed case (OC) data.

Change from Baseline in the CSFQ-14 total score will also be analyzed based on a mixed model for repeated measurements (MMRM) with treatment, center, week, treatment-by-week interaction and sex, as fixed effects, and baseline CSFQ-14 total score, and CSFQ-14 total score-by-week as covariates. The effect at each time point for each treatment is allowed to vary freely and an unstructured covariance matrix is assumed.

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

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

The potential influence of covariates on the primary efficacy analyses will be investigated in ANCOVA model by adding main terms for the covariate as well as interaction terms with treatment. Among the covariates to be investigated are sex, pooled center, race, baseline weight, BMI, and age.

For the primary efficacy variable (using both MMRM and ANCOVA), subgroup analyses by:

- age (≤median, >median).
- sex (female, male).
- race (Caucasian, Non-Caucasian).
- baseline CSFQ-14 total score (≤ median, > median).

and other variables will be performed if each of the subgroups contains at least 20% of the total subjects in the study.

7.9.4 Secondary Efficacy Endpoints

Change from Baseline in CSFQ-14 total score for vortioxetine (10mg and 20mg separately) 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. MMRM method will also be used in sensitivity analyses. 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 both LOCF and OC) during the double-blind Treatment Period will be analyzed by logistic regression, adjusting for baseline CSFQ-14 total score, sex, and treatment.

The following SAS code will be used for the logistic regression analysis:

Proc logistic data=all descending;
- class treat;
- model resp = treat baseline sex;

In the above model, Baseline is the baseline value for the corresponding response variable.

In addition, the sex effect on sexual dysfunction will also be investigated by the inclusion of the sex-treatment interaction term and the sex subgroup analysis.

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

7.9.5 Additional Endpoints

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 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 and time to CSFQ-14 negative response (defined as the decrease from Baseline in CSFQ-14 total score ≥3) will be analyzed using a Cox model with an exact method to handle ties, with treatment and sex as factors. The SAS code for the time-to-event analysis will be as follows:

proc phreg;

- class treat;
- model T_Sexdys*status_1(0) = treat sex/ ties=exact;

The analysis will also be supplemented with plots of Kaplan-Meier estimates of sexual dysfunction.

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. MMRM analysis will also be performed.

7.10 Analyses of Columbia-Suicide Severity Rating Scale (C-SSRS)

The following summaries will be presented for C-SSRS scale in the safety analysis set:

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

7.11 Pharmacokinetic/Pharmacodynamic 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.

7.12 Pharmacogenomic Analyses

A pharmacogenomic analysis plan will be prepared prior to the exploratory pharmacogenomic analysis. This plan will describe the underlying hypotheses, the pharmacogenomic analysis set, genes that will be included in the analysis and the statistical methods to be used.

7.13 Safety Analysis

Safety summaries will be based on the safety set. Conventions for the definition of baseline values and visit windowing are given in Section 7.1.3. 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.

7.13.1 Adverse Events

All adverse events will be coded using MedDRA version 19.0. 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). 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 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:

- Overview of TEAEs during the study - number and percentage of subjects, number of events.

- Pretreatment adverse events by SOC and preferred term.
- 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.
- 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.
- Intensity of Drug-related TEAEs by SOC and preferred term - number and percentage of subjects.
- 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.

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 or related), the outcome (recovered, recovering, not recovered, recovered with sequelae, unknown, or fatal), whether the adverse event was an SAE.

Special listings for TEAEs leading to study discontinuation, SAEs, deaths, and if needed, AE of special interest will also be presented.

7.13.2 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, γ-Glutamyl transferase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, creatine kinase, and total protein.

- 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 specific gravity, pH, protein, glucose, and occult blood.

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 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. Takeda Development Center Americas, Inc ., Protocol No. Vortioxetine-4001 Incorporating Amendment No. 01, dated 10 January 2017, 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), 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 PCS 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 Systeme International (SI) and conventional units.

7.13.3 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.

7.13.4 Vital Signs

Vital signs and weight at scheduled visits and their changes from Baseline will be summarized for each treatment group and overall using descriptive statistics by visit and end of study. 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.

7.13.5 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.

7.13.6 12-Lead ECGs

ECG variables at Baseline will be summarized for each treatment group and overall using descriptive statistics.

7.13.7 Pregnancy Test

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

7.13.8 Skin Rash and Allergic Type Reactions

Any subject who develops a rash will undergo and assessment to characterize the nature and location of the rash. Data collected regarding these reactions will be listed by treatment, study center and subject number.

7.14 Interim Analysis

Not applicable.

7.15 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

1. 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. Takeda Development Center Americas, Inc ., Protocol No. Vortioxetine-4001 Incorporating Amendment No. 01, dated 10 January 2017.

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 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
Uric acid	SI	μmol/L	High: ≥1.3×ULN, Low: ≤0.7×LLN
	conventional	mg/dL	High: ≥1.3×ULN, Low: ≤0.7×LLN
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
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 Arterial Pressure	mmHg	Low: < 85
		High: > 180
Diastolic Arterial Pressure	mmHg	Low: < 50
		High: > 110
Pulse	bpm	Low: < 50
		High: > 120
Body Temperature	^{o}C	Low: < 35.6
		High: > 37.7
	^{o}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.