Title: A Phase 1, Randomized, Open-label, 2-way Cross-over Study to Evaluate the Bioequivalence Between a Single Oral Dose of Esomeprazole 40 mg Capsules and Esomeprazole 40 mg Tablets in Healthy Subjects

NCT Number: NCT03083639

SAP Approve Date: 01 June 2017

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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Esomeprazol-1001

A Phase 1, Randomized, Open-label, 2-way Cross-over Study to Evaluate the Bioequivalence Between a Single Oral Dose of Esomeprazole 40 mg Capsules and Esomeprazole 40 mg Tablets in Healthy Subjects

Esomeprazole Bioequivalence Study

PHASE 1

Version**:** Final

Date**:** 1 June 2017

Prepared by:

PPD

Based on:

Protocol Version: 2

Protocol Date: 07 March 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
λ_z	terminal dispostion rate constant
AE	adverse event
ANOVA	analysis of variance
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration
BMI	body mass index
C_{max}	maximum observed plasma concentration
CI	confidence interval
CL/F	apparent clearance after extravascular administration
ECG	electrocardiogram
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Drug Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
SD	standard deviation
SAE	serious adverse event
SI	International System of Units
SOC	system organ class
$t_{1/2z}$	terminal elimination half-life
t_{max}	time to reach C_{max}
TEAE	treatment-emergent adverse event
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

To determine the bioequivalence of esomeprazole 40 mg tablets and capsules.

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

To determine pharmacokinetic (PK) parameters for each formulation.

4.4 Study Design

This is a phase 1, randomized, open-label, 2-way cross-over study in healthy adult male and female subjects aged 18 to 55 years, inclusive, to evaluate the bioequivalence of a single oral dose of esomeprazole 40 mg capsules (reference [A]) and esomeprazole 40 mg tablets (test [B]).

It is estimated that 52 subjects will be needed to ensure that 48 subjects complete both periods. Screening for potential subjects will occur between 28 and 2 days prior to Day 1. On Day -1, subjects' eligibility will be reconfirmed and eligible subjects will be randomized in a 1:1 ratio to 1 of 2 sequences (AB or BA), which defines the order in which they will receive esomeprazole regimens in Periods 1 and 2. In both periods, subjects will fast for 10 hours prior to study drug administration and refrain from eating until 4 hours after drug administration. Each period will be separated by a minimum 6-day washout period. Blood samples for PK analysis will be drawn up to 10 hours after study drug administration on Day 1 in each period. Subjects will be confined to the phase 1 unit from Day -1 until the end of all assessments on Day 1 of each period.

Given that esomeprazole is a marketed product with a well-characterized safety profile, this study does not include a follow-up evaluation period. In total, the period of evaluation is expected to be a maximum of 36 days (assuming a washout period of 6 days), including the Screening Period.

A schematic of the study design is shown in Figure 4.a. A schedule of assessments is listed in Appendix A.

Figure 4.a Schematic of Study Design

Pretreatment Period		**Period 1 (a)**			**Period 2 (a)**		
Screening (b)	Check-in	Single Dose and PK (c)	Checkout	Washout (d)	Check-in	Single Dose and PK (c)	Checkout
Days -28 to -2	Day -1	Day 1	Day 1	Day 2-6	Day -1	Day 1	Day 1
	Confinement				Confinement		

(a) Subjects will be admitted to the clinic on Day -1 of each period. On Day 1, subjects will be randomized to 1 of 2 sequences of esomeprazole tablet and capsule. Subjects will be discharged from the clinic on Day 1 after dosing and the completion of all scheduled procedures.
(b) For clinical laboratory tests that are required to be taken under fasting conditions, the subject will be asked to return to the unit at a later date under fasting conditions.
(c) PK samples at 0 (predose), and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours postdose.
(d) Minimum 6-day washout between doses. Day -1 of Period 2 could be the sixth day of washout.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints for this study are the PK parameters derived from the plasma concentrations of esomeprazole 40 mg administered via capsule and tablet after a single dose, which include:

- area under the concentration-time curve from time 0 to infinity (AUC_{∞})
- area under the concentration-time curve from time 0 to time t (AUC_t)
- maximum observed concentration (C_{max})

5.2 Secondary Endpoints

Not applicable.

5.3 Additional Endpoints

Additional endpoints for this study are the PK parameters derived from the plasma concentrations of esomeprazole 40 mg administered via capsule and tablet after a single dose, which include:

- time of first occurrence of Cmax (tmax)
- terminal disposition phase half-life (t1/2z)
- apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration (CL/F)
- apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration (Vz/F)
- terminal disposition phase rate constant (λz)
- lag time to first quantifiable concentration (tlag)

6.0 DETERMINATION OF SAMPLE SIZE

The sample size for this study is estimated at 52, which provides an allowance for 4 dropouts.

The sample size was estimated based on variability data from a previous study, using a percent coefficient of variation (%CV) of 28% as the intrasubject variation for the natural logarithm of C_{max} and the assumed true ratio of 0.95 for tablet over capsule. Given the above information, a sample size of 52 subjects provides at least 90% power for concluding bioequivalence for C_{max} and the power for AUCs is greater than 90%.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. The coefficient of variation (%CV) and geometric mean will be included in the summary of continuous data where indicated. Categorical data will be summarized as the number and percentage of subjects in each category.

Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate. Where applicable, confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate and p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. In addition, the actual day relative to the first dose will be presented, where applicable.

All statistical analyses will be performed using the SAS System® Version 9.4.

7.1.1 Study Definitions

There are no study-specific definitions.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF) dosing page. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug}. Study days on or after the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug + 1}.

All protocol-specified study visit dates are defined relative to Study Day 1.

7.1.3 Definition of Study Visit Windows

There will be no visit windowing.

7.1.4 Conventions for Missing Adverse Event Dates

There will be no imputation of incomplete or missing adverse event dates.

7.1.5 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete or missing concomitant medication dates.

7.1.6 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

Plasma concentrations that are below the lower limit of quantification (< LLOQ) will be treated as zero in the summarization of concentration values and derivation of PK parameters.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- Randomized Set: The randomized set will consist of all subjects who are randomized.
- Safety Analysis Set: The safety analysis set will consist of all subjects who are randomized and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.
- Pharmacokinetic Set: The PK set will consist of all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

Number of subjects in each analysis set will be tabulated by randomization sequence and overall.

7.3 Disposition of Subjects

Study Information, including date of first subject signing Informed Consent Form (ICF), date of first/last study drug, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Drug Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary (WHODrug) Version, and SAS Version, will be tabulated.

The eligibility of subjects will be summarized, along with the primary reasons of screen failure as recorded in eCRF.

Number of subjects randomized will be tabulated by randomization sequence (ie AB or BA) and overall.

Disposition of all enrolled subjects will be tabulated. Categories will include:

- Subjects who were randomized but not treated
- Subjects who completed the study
- Subjects who prematurely discontinued study

Primary reasons for discontinuing study, as entered on the eCRF will be tabulated.

7.4 Demographic and Other Baseline Characteristics

Demographic and study baseline characteristics, including age at informed consent, gender, ethnicity, race, height (cm), weight (kg), body mass index (kg/m^2), smoking status, alcohol use, caffeine/xanthine consumption, and female reproductive status, will be summarized by sequence and overall.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that resolved at or prior to the time of informed consent. Concurrent medical conditions are defined as significant conditions or diseases that are present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the MedDRA coding system.

Medical history and concurrent medical conditions will be listed by site and subject number.

There will be no summary or inferential analysis of medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent. Concomitant medication is any drug given in addition to the study drug, taken at any time from signing of informed consent through the end of study.

Medication history and concomitant medications will be coded using the WHODrug.

Listings for medication history and concomitant medications will be produced by site and subject number.

There will be no summary or inferential analysis of medication history and concomitant medications.

7.7 Study Drug Exposure and Compliance

All doses of study medication will be administered during confinement. Dosing data, including dosing time will be provided by subject and visit in the listings.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The schedule for blood samples for PK analysis of Esomeprazole is listed in Table 7.a.

The concentration of esomeprazole in plasma will be summarized by formulation over each scheduled sampling time point using descriptive statistics (arithmetic mean, SD, CV%, median, minimum and maximum). Individual plasma concentration data versus time will be presented in a data listing.

In addition, the figures for mean plasma concentrations of esomeprazole versus time (linear and semi-log scale) will be generated.

Descriptive statistics (N, mean, SD, CV%, median, minimum and maximum) will be used to summarize the PK parameters for Esomeprazole by formulation. In addition, geometric mean will be computed for PK parameters. The PK parameters of Esomeprazole are listed in Table 7.b.

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Esomeprazole	Plasma	1	Predose, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours

Table 7.b Plasma PK Parameters

Symbol/Term	Definition
Plasma	
AUC_t	Area under the concentration-time curve from time 0 to time t
AUC_∞	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
λ_z	Terminal disposition phase rate constant.
$t_{1/2z}$	Terminal disposition phase half-life.
t_{lag}	Lag time to first quantifiable concentration.
t_{max}	Time of first occurrence of C_{max}
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.

Box plots for Cmax and AUC∞ will be generated by formulation.

The bioequivalence between Esomeprazole capsules (Reference - Regimen A) and Esomeprazole tablets (Test - Regimen B) will be assessed for the natural logarithms of AUCt, AUC∞, and Cmax using analysis of variance (ANOVA) models. The models will include regimen, period, and sequence as fixed effects and subject nested within sequence as a random effect. Within the ANOVA framework, point estimates and their 90% CIs for the ratio of AUCs and Cmax central values between Esomeprazole capsules and tablets will be presented. Bioequivalence between tablet and capsule will be claimed if the 90% CI for the ratio is within the bioequivalence criteria of 0.80 to 1.25.

All pharmacokinetic parameters calculated will be provided in a listing.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Daily meals during confinement in each period will be reported in the data listing.

7.11 Safety Analysis

Safety analyses include adverse events (AEs), clinical laboratory parameters, vital sign parameters, and 12-lead electrocardiogram (ECG) results.

All summaries of safety data are based on subjects in the Safety Analysis Set.

7.11.1 Adverse Events

A treatment -emergent adverse event (TEAE) will be defined as an AE or serious adverse event (SAE) that started or worsened after first study drug administration and within 30 days of last dose of study drug (onset date – date of last dose + 1 ≤ 30). A TEAE will be attributed to a regimen if the TEAE occurs after administration of the study drug in a period and up to just prior to study drug administration in the next period. A TEAE that occurs after administration of the study drug in the last period and up to 30 days after the last study drug dose is attributed to the regimen received in the last period. All AE verbatim terms will be coded by system organ class (SOC) and preferred term using (PT) the MedDRA coding system.

TEAEs will be summarized by regimen and overall. The tables will include the number and percentage (N [%]) of subjects reporting any event for that term. The following TEAE tables will be summarized.

- Overview of TEAEs.
- TEAEs by SOC and PT at subject and event level.
- Subject Mappings for TEAEs.
- TEAEs by PT.

- Most Frequent TEAEs by PT term
- Most Frequent Non-Serious TEAEs by PT term at subject and event level
- Relationship of TEAEs to Study Drug by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Severity of TEAEs by SOC and PT.
- Severity of Drug-Related TEAEs by SOC and PT.

In addition, pretreatment events (PTEs) will be summarized overall by SOC and PT.

For each regimen and overall, subjects reporting more than one occurrence for a term (SOC or PT) being summarized will be counted only once using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

Most frequent TEAEs are those events occurred in at least ≥ 5% (before any rounding) of subjects in a regimen.

Data listings will be provided for all TEAEs, PTEs, TEAEs that led to study discontinuation, TEAEs that led to abnormal liver functions, SAEs, AEs that resulted in death, and AEs occurring more than 30 days after the last dose of study medication.

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include hematology, chemistry, urinalysis, and diagnostic screening. Refer to Appendix A for scheduled clinical laboratory test measurements and to Table 7.c for the list of all clinical laboratory tests.

Individual results for hematology and chemistry laboratory tests that meet the Takeda predefined laboratory markedly abnormal value (MAV) criteria in Appendix B will be presented in a data listing. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed.

All clinical laboratory data will be presented in both SI and conventional units in the data listings. Laboratory data outside of the normal reference range will be listed. Out of normal range values and MAVs will be flagged in data listings.

Table 7.c Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	Alanine aminotransferase	pH
WBC (with differential)	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	Aspartate aminotransferase	Ketones
Platelets	Glucose (a)	Glucose
MCHC	Gamma-glutamyl transferase	Bilirubin
MCV	Total bilirubin	Blood
RDW	Total protein	Nitrites
Reticulocyte count	Serum creatinine	Leukocyte esterase
PT/INR	Blood urea nitrogen	Microscopic Analysis (only of positive dipstick result):
aPTT	Phosphorous	RBC/high power field
	Potassium	WBC/high power field
	Chloride	Epithelial cells, casts
	Bicarbonate or carbon dioxide	
	Sodium	

Diagnostic Screening:	
Serum	**Urine**
HIV test Hepatitis panel, including HBsAg and anti-HCV Ab *Female subjects:* Human chorionic gonadotropin (for pregnancy) *Female subjects of child-bearing potential only when menopause is suspected:* Follicle-stimulating hormone	Drug screen, including alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine

anti-HCV Ab=anti-hepatitis C virus antibody, aPTT=activated partial thromboplastin time, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, PT=prothrombin time, RBC=red blood cell, RDW=red cell distribution width, WBC=white blood cell.
(a) Conducted under fasting conditions.

7.11.3 Vital Signs

Refer to Appendix A for scheduled vital signs measurement visits.

Individual results for vital sign measurements that meet the Takeda predefined vital signs MAV criteria in Appendix C will be presented in a data listing. If a subject has a MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix A. The ECG parameters include heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval (Fredericia's and Bazett's corrections).

Individual results for 12-lead ECG measurements that meet the Takeda predefined 12-lead ECG MAV criteria in Appendix D will be presented in a data listing. If a subject has a MAV for a particular ECG parameter, all visits for that subject for that parameter will be listed.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Physical examination findings will be presented in the listings. No summary tables will be provided.

All cases of overdose will be listed.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

1. A Phase 1, Randomized, Open-label, 2-way Cross-over Study to Evaluate the Bioequivalence Between a Single Oral Dose of Esomeprazole 40 mg Capsules and Esomeprazole 40 mg Tablets in Healthy Subjects, Takeda Development Center Europe, Ltd., Protocol No. Esomeprazole-1001, dated 07 March, 2017.

Appendix A Schedule of Study Procedures

	Pretreatment Period		Treatment Periods 1 and 2	Washout (a)	Study Exit / Early Termination
Study Day:	**Days -28 to -2**	**Day -1 (Check-in)**	**Day 1**	**Days 2-6**	**Day 1 of Periods 1 and 2 (prior to Checkout)**
Confinement		X	X		X
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics and medical history	X				
Medication history	X	X			
Physical examination	X	X (b)			X
Vital signs (c)	X	X	X		X
Height, weight and BMI (d)	X	X			
Concomitant medications		X	X	X	X
12-lead ECG	X	X			X
Clinical laboratory tests (e)	X	X			X
Urine drug, alcohol, and cotinine screen	X	X			
Pregnancy test (hCG)	X	X			X
Serum FSH (f)	X				
HIV test	X				
Hepatitis panel	X				
Randomization			X		
Administration of study drug (g)			X		
PK blood collection (h)			X		
Adverse Event assessment (i)	X	X	X	X	X

(a) There will be a minimum 6-day washout period between doses. Day -1 of Period 2 could be the sixth day of washout.
(b) Can be conducted up to 24 hours prior to dosing.
(c) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute) at Screening. Only blood pressure and pulse will be collected on Check-in (Day -1) through Day 1 of each period, or if the subject early terminated from study. On Day 1 of each period, vital signs will be taken at predose.
(d) Height only measured at Screening.
(e) Hematology, serum chemistries, and urinalysis tests.
(f) For women where menopause is suspected.
(g) Study drug administered beginning at approximately 0800 hours.
(h) Blood samples for PK obtained predose (within 15 minutes prior to dose), and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours postdose on Day 1 of each period. The PK sample should not be collected on Early Termination if a PK collection is not scheduled.
(i) Pretreatment adverse events will be captured immediately following the signing of the informed consent at Screening until dosing on Day 1 of Period 1. The routine collection of AEs will continue after dosing through to check out on Period 2, Day 1.

Appendix B Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional SI	<75 x 10^3/μL <75 x 10^9/L	>600 x 10^3/μL >600 x 10^9/L
MCV	Both	<70 fL	>110 fL
Prothrombin time/international normalized ratio	Both	--	>1.5 × ULN
Activated partial thromboplastin time	Both	--	>1.5 × ULN

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional SI	-- --	>2.0 mg/dL >34.2 μmol/L
Albumin	Conventional SI	<2.5 g/dL <25 g/L	-- --
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional SI	--	>2.0 mg/dL >177 μmol/L
Blood urea nitrogen	Conventional SI		>30 mg/dL >10.7 mmol/L
Sodium	Conventional SI	<130 mEq/L <130 mmol/L	>150 mEq/L >150 mmol/L
Potassium	Conventional SI	<3.0 mEq/L <3.0 mmol/L	>6.0 mEq/L >6.0 mmol/L

Parameter	Unit	Low Abnormal	High Abnormal
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Chloride	Conventional	< 75 mEq/L	>126 mmol/L
	SI	< 75 mmol/L	>126 mmol/L
Bicarbonate	Conventional	< 8.0 mEq/L	
	SI	< 8.0 mmol/L	
Phosphorous	Conventional	< 1.6 mg/dL	>6.2 mg/dL
	SI	< 0.52 mmol/L	>2.000 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix C Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	< 35.6	>37.7

Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcB Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	05-Jun-2017 14:06 UTC
	Clinical Science Approval	05-Jun-2017 14:15 UTC
	Pharmacovigilance Approval	06-Jun-2017 09:28 UTC
	Clinical Pharmacology Approval	06-Jun-2017 20:18 UTC
	Statistical Approval	06-Jun-2017 21:32 UTC