Title: A Fixed Sequence, Open-Label, 2-Period Crossover Trial to Evaluate the Effect of the Potent Cytochrome P-450 3A4 Inhibitor Itraconazole on the Pharmacokinetics of TAK-954 in Healthy Adult Subjects

NCT Number: NCT03173170

SAP Approve Date: 08 August 2017

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-954-1004

A Fixed Sequence, Open-Label, 2-Period Crossover Trial to Evaluate the Effect of the Potent Cytochrome P-450 3A4 Inhibitor Itraconazole on the Pharmacokinetics of TAK-954 in Healthy Adult Subjects

PHASE 1

Version: Final

Date: 08 August 2017

Prepared by:

PPD

Based on:

Protocol Version: Original

Protocol Date: 03 May 2017

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

5-HT4	serotonin type 4
β-hCG	β–human chorionic gonadotropin
AE	adverse event
Aet	amount of drug excreted in urine from time 0 to time t
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUClast	area under the concentration-time curve from time 0 to the last measurable time point.
AUCt	area under the concentration-time curve from time 0 to time t.
AUC_{∞}	area under the concentration-time curve from time 0 to infinity.
BMI	body mass index
CFR	Code of Federal Regulations
CLR	renal clearance
C_{max}	maximum observed concentration
CRU	clinical research unit
CV	coefficient of variation
CYP	cytochrome P-450
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
EFI	enteral feeding intolerance
EMA	European Medicines Agency
fe	fraction of administered dose of drug excreted in urine
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HR	heart rate
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose

PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
t1/2	terminal elimination half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the trial is to evaluate the effect of the potent CYP3A4 inhibitor itraconazole on the single-dose PK of TAK-954.

4.2 Secondary Objectives

The secondary objectives of the trial are to evaluate the safety of single-dose IV doses of TAK-954 in the presence and absence of a potent CYP3A4 inhibitor.

4.3 Exploratory Objectives

Exploratory objectives of this trial include:

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[redacted]

4.4 Study Design

This is a phase 1, single-sequence, open-label, 2-period crossover trial in approximately 10 healthy male and female (non–childbearing potential) subjects. The trial is designed to investigate the effect of a potent CYP3A4 inhibitor (itraconazole) on the PK of TAK-954. TAK-954 0.2 mg will be administered as a single 60-minute IV infusion.

The trial will include a Screening Visit, Trial Period 1 (6 days), a washout (a minimum of 7 days between doses in Period 1 Day 1 and Period 2 Day 1), Trial Period 2 (9 days), and a Follow-up Visit.

On Day 1 of Trial Period 1 subjects will receive a 0.2 mg single-dose TAK-954 IV on this day and on Day 4 of Trial Period 2 at approximately the same time (between 0600 and 0900). In Trial Period 2, subjects will receive 200 mg QD itraconazole orally on Days 1 to 8 at approximately the same time (between 0600 and 0900). Itraconazole will be administered as 2 x 100 mg capsules.

Blood samples for assessment of TAK-954 concentrations will be collected before each dose of TAK-954 and at intervals up to 120 hours after the last dose of trial drug in each trial period. Samples may be assayed for TAK-954 metabolites. TAK-954 and its metabolites will also be assayed in urine, data permitting and if deemed possible.

Whole blood samples for DNA PGx analysis and RNA isolation will be collected predose on Day 1of Trial Period 1.

Safety will be assessed by monitoring for AEs, ECGs, vital signs, safety laboratory tests, and physical examinations throughout each dosing period.

CCI [redacted]

After completion of the trial (or after subject withdrawal), all subjects will return for a Follow-up Visit, approximately 10 to 14 days after their last dose of trial drug.

5.0 ANALYSIS ENDPOINTS

The primary endpoint of the trial is the following PK parameters on Day 1 of Trial Period 1 and Day 4 of Trial Period 2:

- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}).

Safety endpoints include the following:

Safety and tolerability will be assessed through physical examinations, ECGs, vital signs, and laboratory assessments, and collection of spontaneous AEs.

Exploratory endpoints will be assessed through the following parameters:

PK parameters:

CCI

[redacted]

Pharmacodynamic parameters:

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 10 subjects will complete this trial. With this sample size, a 2-sided 95.0% CI for the geometric mean ratio of Cmax for TAK-954 when administered with and without itraconazole will have 90% probability of excluding 1.25 (the upper bound of the bioequivalence range) if itraconazole increases the Cmax for TAK-954 by at least 50%. This calculation assumes that the CI is based on the t statistic, that the distance from the mean to the lower bound of the CI on the natural-log scale is 0.182, and that the true SD of differences on the natural-log scale is 0.187 as estimated from Cmax values reported for Cohort 1 in Theravance Protocol No. 0095. Assuming the intrasubject variation observed for area under the concentration-time curve from time 0 to time t in that cohort (SD=0.129), a 2-sided 95.0% CI for the geometric mean ratio of AUC_{∞} for TAK-954 when administered with and without itraconazole will have greater than 99% probability of excluding 1.25 if itraconazole increases AUC_{∞} for TAK-954 by at least 50%.

Subjects who drop out may be replaced at the discretion of the sponsor in consultation with the investigator. Subjects who replace dropouts will begin the trial as a new subject in Trial Period 1.

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}.

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:

- 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.

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.

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

- 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) and body mass index (kg/m^2), will be summarized.

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 at the clinc. Dosing data, including dosing time will be provided by subject and visit in the listings.

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

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Blood samples for PK analysis of TAK-954 are obtained relative to the dose on Day 1 of Period 1 and Day 4 of Period 2 at the following times: predose (within 30 minutes), and 0.33, 0.5, 0.67, 1 (just after the end of infusion), 1.5, 2, 3, 4, 6, 12, 24, 36, 48, 72, 96, and 120 hours postdose (relative to TAK-954 start of infusion).

The concentration of TAK-954 (and metabolites THRX-513466 and THRX-913682) in plasma will be summarized by regimen 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 TAK-954 (and any measured metabolites) versus time (linear and semi-log scale) will be generated.

Urine is collected at predose, 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours relative to TAK-954 infusion start in Trial Periods 1 and 2. The amount of TAK-954 (and any measured metabolites) recovered in urine will be summarized by regimen over each scheduled sampling interval using descriptive statistics (arithmetic mean, SD, CV%, median, minimum and maximum). Individual urine collection information including volume, concentration, and amount recovered will be presented in a data listing.

The plasma PK parameters determined are C_{max}, AUC_{∞}, AUClast, $t_{1/2}$, CL, and Vz. The ratio of metabolite parameter to TAK-954 parameter will also be determined for C_{max} and AUC. The urinary PK parameters determined are Aet, fe, and CLr. Descriptive statistics (N, mean, SD, CV%, median, minimum and maximum) will be used to summarize the PK parameters for TAK-954 (and metabolites THRX-513466 and THRX-913682) by regimen. In addition, geometric mean will be computed for Cmax and AUC parameters. Additional plasma and/or urine PK parameters may be calculated if necessary, in accordance with the Clinical Pharmacology Analysis Plan (CPAP). All pharmacokinetic parameters calculated will be provided in a data listing.

Box plots for C_{max} and AUC_{∞} will be generated by regimen.

For evaluation of potential effect of itraconazole on TAK-954 PK, paired t-tests and associated CIs will be determined on the natural logarithms of C_{max} and area under the concentration-time curve (AUC_{∞} and AUC_{last}) to assess the exposure between regimens (TAK-954 alone and TAK-954 with itraconazole). This paired t-test (one-sample t-test) will be performed on the differences (TAK-954 with itraconazole minus TAK-954 alone) of the natural logarithm transformed parameters for the two regimens. The relative bioavailability estimate and the 90% confidence intervals for relative bioavailability will be obtained by exponentiating the estimated difference and the 90% confidence intervals for the estimated difference between regimens in the log-transformed parameters.

Additional analyses may be performed if appropriate.

7.9.2 Pharmacodynamic Analysis

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[redacted]

7.10 Other Outcomes

Not Applicable.

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 (TAK-954 alone, itraconazole alone, and TAK-954 with itraconazole) 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.
- 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).

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 for this study are listed below. The schedule of clinical laboratory collections is presented in Appendix A.

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.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Bicarbonate	Chloride
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above ULN, will be fractionated
Protein (total)	

Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells [RBCs])	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells [WBCs]) with absolute differential	

Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

7.11.3 Vital Signs

Vital sign measurements include body temperature, pulse, respiratory rate, and blood pressure. 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, PR interval, QRS interval, QT interval, and QTc interval (Fredericia's correction).

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 information 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

Appendix A Schedule of Study Procedures

Assessment	Screening	Trial Period 1 (a)					Trial Period 2									Follow-up/Early Termination
Day	-28 to -2	-1	1	2	3	4 to 6	-1	1	2 to 3	4	5	6	7	8	9	10-14 days after last dose of trial drug
Administrative Procedures																
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Medical history/demographics	X															
Prior and concomitant medication review	----------Continuous review----------															
Clinic Procedures/Assessments																
Full physical examination	X	X														X
Semirecumbent vital signs (heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]	X		X(b)	X	X		X	X	X	X (b)	X	X			X	X
Vital signs (respiratory rate, oral [at the floor of the mouth]/tympanic temperature) rate	X		X(b)				X									
Height	X															
Weight	X															
Body mass index (BMI)	X															
Standard 12-lead electrocardiogram (ECG)	X		X(b)		X		X			X (b)					X	X
Bowel movement assessment (c)			X	X	X			X	X	X						
Adverse event (AE) monitoring	----------Continuous review----------															
Laboratory Procedures/Assessments																
Serum chemistry	X	X			X		X							X		X
Hematology	X	X			X		X							X		X
Urinalysis	X	X			X		X							X		X
Serum follicle-stimulating	X															

Appendix A Schedule of Study Procedures (continued)

Assessment	Screening	Trial Period 1 (a)					Trial Period 2									Follow-up/Early Termination
Day	-28 to -2	-1	1	2	3	4 to 6	-1	1	2 to 3	4	5	6	7	8	9	10-14 days after last dose of trial drug
hormone (FSH)																
Urine drug screen	X	X					X									
Urine alcohol test/alcohol breath test (d)	X	X					X									
HIV test	X															
Hepatitis panel	X															
Pharmacokinetics (PK) Evaluations																
Plasma samples for TAK-954 (e)			X	X	X	X				X	X	X	X	X	X	
Urine sample for TAK-954 PK (f)			X	X	X					X	X	X				
Pharmacogenomic (PGx) Evaluations																
Blood sample for DNA PGx			X													
Blood sample for RNA PGx			X													
Drug Administration																
TAK-954 dosing			X							X						
Itraconazole dosing								X	X	X	X	X	X	X		
Other																
Confinement		X	X	X	X			X	X	X	X	X	X			
Meals		X	X	X	X		X	X	X	X	X	X	X			

(a) A minimum of 7 days between doses in Period 1 Day 1 and Period 2 Day 1.
(b) Assessments at predose (within 30 minutes), 1, 2, 4, 8, and 12 hours postdose (relative to TAK-954 start of infusion).
(c) Bowel movement assessment will include first bowel movement, stool consistency (Bristol Stool Scale), and frequency of bowel movements.
(d) An alcohol breath test may be performed at the discretion of the investigator.
(e) Time points for PK blood samples for TAK-954: predose (within 30 minutes), and 0.33, 0.5, 0.67, 1 (just after the end of infusion), 1.5, 2, 3, 4, 6, 12, 24, 36, 48, 72, 96, and 120 hours postdose (relative to TAK-954 start of infusion).
(f) Urine collected at predose, 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours relative to TAK-954 infusion start in Trial Periods 1 and 2.

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

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
Glucose	Conventional SI	< 50 mg/dL < 2.8 mmol/L	>350 mg/dL >19.4 mmol/L
Chloride	Conventional SI	< 75 mEq/L < 75 mmol/L	>126 mmol/L >126 mmol/L
Bicarbonate	Conventional SI	< 8.0 mEq/L < 8.0 mmol/L	
Calcium	Conventional SI	< 7.0 mg/dL < 1.75 mmol/L	>11.5 mg/dL >2.88 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 Markedly Abnormal 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
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
PR	≤120 milliseconds	≥200 milliseconds
QRS	≤60 milliseconds	≥120 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	11-Aug-2017 16:30 UTC
	Clinical Pharmacology Approval	11-Aug-2017 16:36 UTC
	Statistical Approval	11-Aug-2017 16:38 UTC
	Pharmacovigilance Approval	17-Aug-2017 13:05 UTC
	Biostatistics Approval	17-Aug-2017 13:07 UTC