Title: A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects

NCT Number: NCT03101293

SAP Approve Date: 09 June 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.

**TAKEDA DEVELOPMENT CENTER**

# STATISTICAL ANALYSIS PLAN

**STUDY NUMBER: TAK-831-1004**

A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects

**Phase 1, Food Effect Study of TAK-831**

**PHASE 1**

Version**:** Final V1.0

Date**:** 09 June 2017

**Prepared by:**

PPD

**Based on:**

Protocol Version: Amendment 01

Protocol Date: 11 April 2017

## 1.1 Approval Signatures

**Study Title:** A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects

**Takeda Approvals:**

| | |
|---|---|
| PPD | Date |
| PPD | Date |
| PPD | Date |
| PPD | Date |
| PPD | Date |

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## 3.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| %CV | percent coefficient of variation |
| ADaM | Analysis Data Model |
| AE | adverse event |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| $AUC_{\infty}$ | area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty}=AUC_{last}+C_{last}/\lambda_z$ |
| $AUC_{last}$ | area under the plasma concentration-time curve from time 0 to last quantifiable concentration |
| AUEClast | area under the effect-time curve from time 0 to the last scheduled post dose time point (last = 168 h) |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| CI | confidence interval |
| CL/F | apparent clearance after extravascular administration, calculated as CL/F =Dose/$AUC_{\infty}$ after a single dose |
| $C_{max}$ | maximum observed plasma concentration |
| ECG | electrocardiogram |
| eCRF | electronic case report forms |
| $E_{max}$ | maximum observed effect |
| LS | least squares |
| MAV | markedly abnormal value |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N | number of subjects |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PT | preferred term |
| PTE | pretreatment event |
| QTcF | QT interval with Fridericia correction method |
| Residual Area | postulated area: ($AUC_{\infty}$ - $AUC_t$)/$AUC_{\infty}$ |
| $t_{1/2z}$ | terminal elimination half-life, calculated as $\ln(2)/\lambda_z$ |
| TEAE | treatment-emergent adverse event |
| time to Emax | time to reach maximum observed effect |
| $t_{max}$ | time to reach $C_{max}$ |
| $V_z/F$ | apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$ |
| WHO Drug | World Health Organization Drug Dictionary |
| $\lambda_z$ | terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase |

# 4.0 OBJECTIVES

## 4.1 Primary Objective

- To determine the PK of a single oral dose of TAK-831 400 mg in the fasted state and to estimate the effect of food on the PK of a single oral dose of TAK-831 400 mg when administered as the T2 tablet formulation in healthy subjects.

## 4.2 Secondary Objective

- To evaluate the safety and tolerability of a single oral dose of TAK-831 400 mg in healthy subjects in the fed and fasted states.

## 4.3 Exploratory Objective

CCI [redacted]

## 4.4 Study Design

TAK-831-1004 is a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the PK of TAK-831 400 mg and assess the effect of food on the bioavailability of TAK-831 400 mg, when administered as four 100 mg oral tablets of the T2 formulation in healthy male and female adult subjects. At Check-in (Day -1) of Period 1, 16 healthy male and female subjects, aged 18 to 55 years, inclusive, who meet the study entry criteria will be enrolled in the study. On Day 1 of Period 1, eligible subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences, which will define the order in which they will receive the TAK-831 regimens in Periods 1 and 2 (Figure 4.a). Dosing between periods will be separated by a washout interval of ≥7 days.

**Figure 4.a Study Treatment Sequences**

| Treatment Sequence | Number Of Subjects | Regimen | |
|---|---|---|---|
| | | Period 1 | Period 2 |
| 1 | 8 | A | B |
| 2 | 8 | B | A |

Regimen A=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1 with water;
Regimen B=a single oral dose of 4 TAK-831 100 mg tablets (T2 formulation; total dose 400 mg) administered on Day 1, 15 minutes after starting ingestion of Ensure Plus. For both regimens, subjects will fast for ≥10 hours overnight before dosing.

The study will include a Screening Period (Days -28 to -2), 2 treatment periods, and a Follow-up Phone Call (14±2 days after last dose of study drug). In each period, subjects will be admitted to the clinic on Day -1 (Check-in) and will remain confined to the clinic until completion of study procedures on the morning of Day 3. Subjects will return to the clinic for study assessments on Days 4, 6, and 8 in each period. Subjects will receive a single dose of TAK-831 on Day 1 of each

period. Blood samples will be collected over 72 hours post dose to measure plasma concentrations of TAK-831 for PK assessments in each period. CCI [redacted] CCI [redacted] CCI [redacted]. Safety will be evaluated throughout the study.

A schematic of the study design is shown in Figure 4.a. A schedule of study procedures is provided in Appendix A of the protocol.

**Figure 6.a Schematic of Study Design**

| Screening | Treatment Periods 1 and 2 | | | | Study Exit | Follow-up (a) |
|---|---|---|---|---|---|---|
| | Check-in and Predose Assessments | Dosing and Study Assessments | PK, PD, and Safety Assessments | | | |
| Days -28 to -2 | Day -1 | Day 1 (b) | Days 1 to 3 | Days 4 to 8 | Period 2 Day 8 (Study Day 16) | Study Day 23 (±2) |
| | Confinement (c) | | | | | |

(a) The Follow-up Visit will occur (14 days after the last dose of study drug) by telephone unless abnormal, clinically significant findings were observed at Study Exit. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.
(b) Subjects will be randomly assigned to 1 of 2 treatment sequences before dosing on Day 1 of Period 1. A washout interval of ≥7 days will separate the dose in Period 1 from the dose in Period 2.
(c) Subjects will be discharged from the clinic after the Day 3 study assessments have been completed and will return to the clinic on Days 4, 6, and 8 for study assessments.

# 5.0 ANALYSIS ENDPOINTS

## 5.1 Primary Endpoints

The following PK parameters of TAK-831 derived for each regimen:

- Maximum observed plasma concentration ($C_{max}$).
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration ($AUC_{last}$).
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{\infty}$).

## 5.2 Secondary Endpoints

- Percentage of subjects who experience at least 1 TEAE.

## 5.3 Exploratory Endpoints

The following additional safety endpoints:

- Percentage of subjects who meet the markedly abnormal criteria for clinical laboratory tests at least once post dose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post dose.
- Percentage of subjects who meet the markedly abnormal criteria for 12-lead ECG parameters at least once post dose.

The following PK parameters for TAK-831 for each regimen:

- $t_{max}$.
- $t_{1/2z}$.
- CL/F.
- $V_z$/F.

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## 6.0 DETERMINATION OF SAMPLE SIZE

With a sample size of 16 subjects (8 subjects per treatment sequence), allowing for a maximum of 2 dropouts, a 2-sided 90% CI for the difference in the paired means of the $\ln C_{max}$ will extend 0.23 from the observed mean. Assuming a point estimate of the food effect of 2 (observed ratio of fed vs. fasting $C_{max}$=2), which means food increases $C_{max}$ by 100%, this should lead to a lower bound of the 90% CI of 1.589 (58.9% increase) and an upper bound of the 90% CI of 2.517 (151.7% increase) for the ratios of the $C_{max}$ central values (fed/fast). In addition, when a central value ratio of 1 is observed, the 90% CI should be approximately (-0.79, 1.26). This calculation also assumes the intrasubject %CV for $C_{max}$ is 37.5%, which is estimated from Study TAK-831-1001 (Part 4).

# 7.0 METHODS OF ANALYSIS AND PRESENTATION

## 7.1 General Principles

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 [2] and E9 [3] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP was developed using the information provided in Protocol TAK-831-1004, dated 11 April 2017 [1].

All study-related raw data, including derived data, will be presented in data listings. Continuous data will be summarized using: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, %CV and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

### 7.1.1 Missing Data

There will be no imputation of incomplete or missing data. Decisions regarding inclusion or exclusion of data from an analysis for subjects who are noncompliant with the dose schedule, or who have incomplete data, will be made on a case-by-case basis, but the data will be presented in data listings regardless.

Plasma concentrations that are below the limit of quantification (BLQ) will be given a value of 0 in the summarization of concentrations and derivation of the PK parameters. These values will be flagged in the data listings, and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

### 7.1.2 Derived Datasets and Variables

Derived datasets will be generated according to CDISC guidance documents: Analysis Data Model (ADaM) Implementation Guide, Version 1.1 (12 Feb 2016); ADaM Data Structure for Adverse Event Analysis, Version 1.0 (10 May 2012).

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### 7.1.3 Definition of Study Days and Baseline

For safety labs, vital signs and ECGs, Baseline is defined as the last nonmissing measurement prior to first dose of study drug for the respective period. For all other safety endpoints, Baseline is defined as the last nonmissing measurement prior to the first dose of study drug in Period 1. Study day prior to the first dose of study drug will be calculated as: date of assessment/event – date of first dose of study drug; study day on or after the date of first dose of study drug will be calculated as: date of assessment/event – date of first dose of study drug + 1.

## 7.2 Analysis Sets

| | |
|---|---|
| **Safety Analysis Set** | The safety analysis set will consist of all randomized subjects who received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, other baseline characteristic, and safety summaries. |
| **PK Analysis Set** | The PK analysis set will consist of subjects from the safety set who have at least 1 measurable post dose TAK-831 plasma concentration. |
| **PD Analysis Set** | CCI [redacted] |

## 7.3 Disposition of Subjects

The number and percentage of subjects who complete study drugs and study visits, and those who prematurely discontinue study drugs and study visits will be summarized for each sequence and overall. In addition, the number and percentage of subjects will be summarized for reasons of study drug discontinuation and study visit discontinuation for each sequence and overall. Subjects' study completion data, including reasons for premature termination, will be listed.

The number and percentage of subjects comprising each analysis set will be summarized for each sequence and overall.

## 7.4 Demographic and Baseline Characteristics

Demographic and other baseline characteristic data will be listed and summarized for all enrolled subjects by treatment sequence and overall. Summary statistics (eg, N, mean, median, SD, minimum and maximum) will be generated for continuous variables (eg, age and weight), and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race).

Demographic data and reasons for screen failure will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent and reason for screen failure will also be presented in the data listings.

## 7.5 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions that are present at signing of informed consent.

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No summary statistics for medical history and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

## 7.6 Medication History and Concomitant Medications

Medication history information obtained includes any medication stopped at or within 28 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO Drug). No summary statistics for medication history and concomitant medications will be provided. All medication history and concomitant medications data will be listed.

## 7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing. Daily meals during confinement in each period will be reported in the data listing. Summary statistics for TAK-831 plasma concentrations and pharmacokinetic parameters will be provided. No summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

## 7.8 Efficacy Analysis

Not applicable.

## 7.9 Pharmacokinetic Analysis

### 7.9.1 Plasma Concentrations

Serial blood samples for determination of plasma concentrations of TAK-831 will be collected according to the table below:

| Analyte | Matrix | Dosing Day (Period 1 and 2) | Scheduled Time (hours) |
|---|---|---|---|
| TAK-831 | Plasma | 1 | Pre-dose (0 hour, within 15 minutes prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48 and 72 hours post dose |

The concentration of TAK-831 in plasma will be summarized by regimen at each scheduled sampling time using descriptive statistics (N, mean, median, SD, %CV, minimum, and maximum). Individual plasma concentration data versus time will be presented in a data listing.

### 7.9.2 Plasma Pharmacokinetic Parameters

The pharmacokinetic (PK) parameters of TAK-831 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated from the plasma concentration values of TAK-831 using non-compartmental analysis using Phoenix WinNonLin (version 6.3 or higher): $AUC_{last}$, $AUC_{\infty}$, $C_{max}$, CL/F, $\lambda_z$, $t_{1/2z}$, $t_{max}$ and $V_z/F$.

Additional parameters may be calculated if necessary.

For each regimen, descriptive statistics (N, mean, median, SD, %CV, minimum, and maximum) will be used to summarize TAK-831 plasma PK parameters. In addition, geometric means will be calculated for $C_{max}$ and AUCs. Individual subject plasma PK parameter data will be listed.

Statistical inference to estimate the food effect on TAK-831 PK will be performed using an analysis of variance (ANOVA) model on TAK-831 $lnC_{max}$ and lnAUCs. The models will include sequence, period, and regimen as fixed factors and subject-within-sequence as a random factor. Difference between the test regimen (Regimen B: fed state) and the reference regimen (Regimen A: fasted state) will be calculated using the least square (LS) means and 90% C.Is.

To evaluate the effect of food on TAK-831 PK, the central value ratios and the 2-sided 90% CIs for the ratio of the central values for $C_{max}$ and AUCs between the two regimens will be obtained as the antilog of the difference of the least squares (LS) means on a natural logarithm scale, and the 90% CIs will be obtained by taking the antilog of the 90% CI for the difference between the LS means on the natural logarithmic scale.

Alternative statistical analyses will be used if deemed appropriate.

## 7.10 Pharmacodynamic Analysis

### 7.10.1 D-Serine and L-Serine Plasma Concentrations

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[redacted]

CCI

[redacted]

### 7.10.2 Plasma PD Parameters

CCI

[redacted]

CCI

[redacted]

Alternative statistical or PK/PD analyses will be used if deemed appropriate.

## 7.11 Other Outcomes

Not applicable.

## 7.12 Safety Analysis

All safety summary tables will be presented by regimen for all subjects in the safety analysis set. No statistical testing will be performed or inferential statistics will be generated. All CRF collected data will be listed, including: CSSRS, Investigational Drug Overdoses, Physical Examinations, pharmacogenomics sampling times and Telephone Follow-Up Assessments.

### 7.12.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. TEAEs with onset occurring after first dose of study drug and within 30 days (onset date – last date of dose +1≤30) after the last dose of study drug be included in the summary tables.

The TEAE summary tables will include numbers and percentages of subjects experiencing at least one TEAE by SOC and PT and will be tabulated by regimen The TEAE will also be summarized for all subjects in the overview assessment. The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs.
- TEAEs by SOC and PT
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Most Frequent TEAEs by PT.
- Most Frequent Non-Serious TEAEs by PT.
- Drug-Related TEAEs by SOC and PT.
- Relationship of TEAEs to Study Drug by SOC and PT (related vs not related).
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.

Additional AE summary tables may be added as appropriate.

Data listings will be provided for all AEs including PTE, TEAEs, and AEs leading to death, AEs leading to study drug or study visit discontinuation, SAEs and signs and symptoms of AEs related to increased liver function tests.

### 7.12.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. The samples for these tests are collected at Screening, Check-in Period 1, Day 3 Period 1, Check-in

Period 2 (Day -1 of Period 2; also Day 8 of Period 1), and Day 3 Period 2 and Study Exit (Day 8 of Period 2 or Early Termination).

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical laboratory tests will be summarized for baseline, post dose (Days 3 and 8), and change from baseline to post dose by regimen. The Baseline for each regimen is defined as the last observation prior to the dose of study drug in the corresponding period. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for clinical laboratory test will be evaluated against the Takeda predefined laboratory markedly abnormal values (MAV) criteria (Appendix A) using the result and criteria in SI units. All subjects with at least 1 post dose laboratory result that meets the MAV criteria will be presented in a data listing. The number and percentage of subjects with at least 1 post dose markedly abnormal laboratory test result will also be summarized by regimen. Subjects who meet the MAV criteria will be mapped to their respective qualifying laboratory result. All post dose clinical lab MAV results, including scheduled and unscheduled measurements will be included in the MAV summaries.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

### 7.12.3 Vital Signs

Vital sign measurements include body temperature, respiratory rate, blood pressure, and heart rate (beats per minute). Vital signs are measured at Screening, Check-in Period 1, Day 1 (within 50 minutes before dosing and at 1, 4, and 12 hours post dose), 2, 3, 4 and 6 of each period, Check-in Period 2 (also Day 8 of Period 1) and at Study Exit (Day 8 of Period 2 or Early Termination).

Descriptive statistics (N, mean, median, SD, minimum and maximum) of vital signs in each position (supine, standing and orthostatic change for blood pressure and heart rate) will be summarized for baseline, post dose, and change from baseline to post dose by regimen. The Baseline for each regimen is defined as the last observation prior to the dose of study drug in the corresponding period. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

All individual vital signs that meet Takeda's predefined criteria for MAVs (Appendix B) will be listed. The number and percentage of subjects with at least 1 post dose markedly abnormal vital sign measurement will be summarized by regimen. Subjects who meet the MAV criteria will be mapped to their respective qualifying vital sign result. All post dose MAV vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

### 7.12.4 12-Lead ECGs

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The

following parameters will be calculated automatically by the ECG machine: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT interval with Bazett and Frederica correction method (QTcB and QTcF, respectively). ECGs will be obtained at Screening, Check-in Period 1, Day 1 (1, 2 and 4 hours post dose) of Period 1 and 2, Check-in Period 2 (Day 8 of Period 1) and Study Exit (Day 8 of Period 2 or Early Termination).

Descriptive statistics of the continuous ECG parameters will be summarized for baseline, post dose, and change from baseline at each post dose time point by regimen. The Baseline for each regimen is defined as the last observation prior to the dose of study drug in the corresponding period. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed ECG parameters.

All individual ECGs that meet Takeda's predefined criteria for MAVs (Appendix B) will be listed. The number and percentage of subjects with at least 1 post dose markedly abnormal ECG measurement will be summarized by regimen. Subjects who meet the MAV criteria will be mapped to their respective qualifying ECG result. All post dose MAV ECG parameters, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

Individual subject ECGs will be presented in a data listing.

### 7.12 Interim Analysis

Not applicable.

### 7.13 Changes in the Statistical Analysis Plan

Not applicable.

## 8.0 REFERENCES

1. Protocol: A Randomized, Open-Label, Single-Dose, 2-Period, Crossover Design, Phase 1 Study to Evaluate the Effect of Food on the Pharmacokinetics of TAK-831 T2 Tablet Formulation in Healthy Subjects Amendment 01, 11 April 2017.
2. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
3. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.

# Appendix A 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 | <75 x $10^3$/μL | >600 x $10^3$/μL |
| | SI | <75 x $10^9$/L | >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 | -- | >2.0 mg/dL |
| | SI | -- | >34.2 μmol/L |
| Albumin | Conventional | <2.5 g/dL | -- |
| | SI | <25 g/L | -- |
| Total protein | Both | <0.8x LLN | >1.2x ULN |
| Creatinine | Conventional | -- | >2.0 mg/dL |
| | SI | | >177 μmol/L |
| Blood urea nitrogen | Conventional | | >30 mg/dL |
| | SI | | >10.7 mmol/L |
| Sodium | Conventional | <130 mEq/L | >150 mEq/L |
| | SI | <130 mmol/L | >150 mmol/L |
| Potassium | Conventional | <3.0 mEq/L | >6.0 mEq/L |
| | SI | <3.0 mmol/L | >6.0 mmol/L |
| CPK | Both | -- | >5x ULN |
| Glucose | Conventional | <50 mg/dL | >350 mg/dL |
| | SI | <2.8 mmol/L | >19.4 mmol/L |

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

## Appendix B Criteria for Markedly Abnormal Values for 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 |

## Criteria for Identification of Markedly Abnormal Orthostatic Changes

| Parameter | Criteria |
|---|---|
| Orthostatic Hypotension | (Orthostatic Systolic Blood Pressure <-20 mm Hg OR Orthostatic Diastolic Blood Pressure <-10 mm Hg) AND Heart Rate Increase >20 beats/min |

Note: Orthostatic measurement = standing vital measurement – supine vital measurement.

## Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

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

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| PPD | Biostatistics Approval | 09-Jun-2017 20:16 UTC |
| | Clinical Approval | 09-Jun-2017 22:54 UTC |
| | Clinical Pharmacology Approval | 09-Jun-2017 23:23 UTC |
| | Clinical VP Approval | 09-Jun-2017 23:36 UTC |
| | Pharmacovigilance Approval | 12-Jun-2017 19:48 UTC |