



Title: A Randomized, Open-Label, Single-Dose, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin (25 mg) and Pioglitazone (15 and 30 mg) When Administered as Individual Tablets and as Fixed-Dose Combination Tablets to Healthy Russian Subjects

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Alogliptin-1002

A Randomized, Open-Label, Single-Dose, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin (25 mg) and Pioglitazone (15 and 30 mg) When Administered as Individual Tablets and as Fixed-Dose Combination Tablets to Healthy Russian Subjects
Bioequivalence Study of Medicinal Product – SYR-322-4833 BL

PHASE 1

Version: **1.0**

Date: 20 June 2018

Prepared by:

PPD

A large blue rectangular redaction box covers the name and contact information of the person who prepared the document.

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1.1 Approval Signatures

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

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3.0 LIST OF ABBREVIATIONS

| | |
|------------------|--|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BMI | body mass index |
| C _{max} | maximum concentration |
| CPK | creatine phosphokinase |
| CV | coefficient of variation |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| GGT | γ-glutamyl transferase |
| ICF | informed consent form |
| HIV | human immunodeficiency virus |
| LLN | lower limit of normal |
| MAV | markedly abnormal value |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PK | pharmacokinetics |
| SAE | serious adverse event |
| ULN | upper limit of normal |
| WHODrug | World Health Organization Drug Dictionary |

4.0 OBJECTIVES

4.1 Primary Objectives

To assess the relative bioavailability and bioequivalence of 2 strengths of the fixed-dose combination tablet product SYR-322-4833 BL compared to the individual alogliptin and pioglitazone tablets in healthy Russian subjects

4.2 Secondary Objectives

None

4.3 Additional Objectives

To perform a comparative analysis of AE data after the administration of SYR-322-4833 BL and after coadministration of alogliptin and pioglitazone to healthy volunteers within the scope of the trial.

4.4 Study Design

This is a single-center, open-label, randomized, 4-sequence, 4-period, single dose crossover study involving 72 healthy adult, male and female subjects between the ages of 18 and 55 years, inclusive.

Subjects will be randomized in the order in which they are enrolled into the study. The 72 eligible subjects will be randomized to 1 of 4 drug intake sequences in a 1:1:1:1 ratio. Due to the large sample size, volunteers may be divided into 2 or 3 cohorts according to space limitations at the site. All cohorts will be dosed sequentially.

The study consists of a Screening Period (Days -28 to Day-2) and 4 Drug Intake Periods. A washout interval of 7 days (beginning immediately after dosing on Day 1) will separate the doses of each study period. Subjects will be admitted into the clinic on Day -1 (Day 7 of the preceding period for Periods 2, 3, and 4) and will be dosed on Day 1 of each period. Starting on Day 1 of each period, blood samples for determination of alogliptin and pioglitazone plasma concentrations will be collected predose through 72 hours postdose. The subjects will be discharged from the clinic after the 24-hour blood sample collection on Day 2 of each period and will return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures. Final Visit procedures will be performed on Day 4 of Period 4 and a Follow-up call will be made 14 days \pm 2 days following the last dose of study drug.

A schematic of the study design is included as [Figure 1](#). A schedule of assessments is listed in [Appendix A](#).

Figure 1 Schematic of Study Design

| Predose Period | | | Drug Intake Period (c) | | | | | | | |
|----------------|--------------|---------------------|------------------------|----------------------|--------------|----------------------|--------------|----------------------|------------------|-------------|
| Screening (a) | Check-in (b) | | Period 1 | | Period 2 | | Period 3 | | Period 4 | |
| Days -28 to -2 | Day -1 | | Day 1 Dosing | Days 2 to at least 7 | Day 1 Dosing | Days 2 to at least 7 | Day 1 Dosing | Days 2 to at least 7 | Day 1 (d) Dosing | Days 2 to 3 |
| | | Sequence I (n=18) | A | WO | B | WO | C | WO | D | WO |
| | | Sequence II (n=18) | B | | C | | D | | A | |
| | | Sequence III (n=18) | C | | D | | A | | B | |
| | | Sequence IV (n=18) | D | | A | | B | | C | |

A=SYR-322-4833 BL (25 mg + 15 mg) (test regimen), B=alogliptin 25 mg + pioglitazone 15 mg (reference regimen), C=SYR-322-4833 BL (25 mg + 30 mg) (test regimen), D=alogliptin 25 mg + pioglitazone 30 mg (reference regimen), ET=Early Termination, WO=Washout of 7 days between dosing.

(a) Screening may consist of 1 or more visits. Subjects will sign an informed consent form at the first visit and return to the clinic in a fasted state for safety laboratory testing at the second visit.

(b) Subjects are admitted into the clinic on Day -1 of each period (~Day 7 of the preceding period for Periods 2, 3, and 4).

(c) Randomization occurs on Day 1 of Period 1. Subjects check out of the unit on Day 2 following the 24-hour blood sample collection but return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures.

(d) Follow-up call will be made 14 days ±2 days following the last dose of study drug.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following plasma pharmacokinetic (PK) parameters of alogliptin and pioglitazone will be derived on Day 1 of each period:

- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from the time 0 to time 72 hours (AUC_{72}).

5.2 Additional Endpoints

- CCI [REDACTED]
- Percentage of subjects who experience at least 1 postdose AE.
- Percentage of subjects who have clinically significant changes in laboratory tests at least once postdose.
- Percentage of subjects who have clinically significant changes in vital sign measurements at least once postdose.
- Percentage of subjects who have clinically significant changes in electrocardiogram (ECG) parameters at least once postdose.
- Percentage of subjects who experience at least 1 postdose event of hypoglycemia.

6.0 DETERMINATION OF SAMPLE SIZE

A sample size of 72 subjects (18 per sequence) will be enrolled in this 4-period, 4-sequence crossover study. The sample size is appropriate to assess the bioavailability of alogliptin and pioglitazone from the fixed dose combination relative to the individual tablets and also provide greater than 80% power for C_{\max} of pioglitazone establishing bioequivalence between regimens for both strengths (SYR-322-4833 BL 25 mg+15 mg and SYR-322-4833 BL 25 mg+30 mg). This is based on acceptance ranges of 80% to 125%, the intra-subject variability (%CV) of 33% for C_{\max} of pioglitazone; the expected ratios of the central values for C_{\max} are between 0.95 and 1.05, and drop-out rate of 14%. Since the intra-subject variability for pioglitazone AUC_t , and alogliptin C_{\max} and AUC_t is less than 33%, the power for assessing bioequivalence for pioglitazone AUC_t and alogliptin C_{\max} and AUC_t are each greater than 80% for both strengths.

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 tabulated as the number and percentage of subjects in each category; unless otherwise specified the denominator for percentage is total number of subjects with non-missing data.

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

Generally, Baseline is defined as the value or observation prior to first dose of study drug, i.e. Day 1 Period 1. Where applicable, pre-dose values will be obtained for each dosing Period.

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}. The calculation of day within a period will be similar to study day but relative to the date of administration of the first dose of study drug within the period.

7.1.3 Definition of Study Visit Windows

All blood samples should be identifiable by date and time. If actual time is missing then the nominal time may be used in the analyses. Safety laboratory collections (i.e. clinical laboratory evaluations) are obtained Pre-dose on Day 1 (baseline) and Day 4 of Period 4 (post-baseline). If a subject has more than one laboratory value (eg. a repeat laboratory draw) then the latter will be used for data analyses.

7.1.4 Conventions for Missing Adverse Event Dates

Missing AE dates will not be imputed. In the event an AE is missing onset date information a consistent and reasonable effort will be made to associate the event to one of the 4 regimens in the study. A few illustrative examples follow:

- Onset date is missing and event stop date predates Day 1 then the event will be evaluated as pre-treatment.
- Onset date is missing and event stop date is within Period X, then AE will be associated with the regimen for Period X.
- Onset date is partial, day missing month available. Then the event will be associated to the Regimen given in earliest Period compatible for the month of onset.

7.1.5 Conventions for Missing Concomitant Medication Dates

Missing dates for concomitant medication will not be imputed. However, if necessary, similar strategies as described in section 7.1.4 will be used to associate the concomitant medication to the trial periods/regimens.

7.2 Analysis Sets

The **safety set** will include all randomized subjects who receive at least 1 dose of study medication, including subjects who do not complete the study. Subjects in this set will be used for demographic and baseline characteristics as well as safety summaries.

The **PK set** will consist of all subjects in the safety set who have sufficient plasma concentration data to facilitate the derivation of at least 1 PK parameter. Details regarding how to handle missing data will be predefined in the Clinical Pharmacology Analysis Plan.

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 used for creating the datasets, will be summarized.

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 treatment sequence 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 first dose administration, sex, ethnicity, race, height (cm), weight (kg), and body mass index (kg/m^2), will be summarized by sequence and overall. Demographic and baseline characteristics variables will not be analyzed inferentially. Demographic variables for subjects screen but not randomized, i.e. screen failure, will be summarize similarly.

7.5 Medical History and Concurrent Medical Conditions

Medical history, defined as significant conditions or diseases that resolved at or prior to the time of informed consent, and concurrent medical conditions, defined as significant conditions or diseases that are present at signing of informed consent, will be coded using the MedDRA coding system. Medical history and concurrent medical conditions will be listed by 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 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. Data on eCRFs for meals received will also be provide in the data 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 alogliptin and pioglitazone is listed in Table 1.

The concentration of both alogliptin and pioglitazone 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 listed. In addition, the figures for mean plasma concentrations of alogliptin (pioglitazone) versus time (linear and semi-log scale) will be generated.

PK parameters for alogliptin and pioglitazone will be estimated using non-compartmental methods. Additional details concerning the calculation and reporting of PK parameters can be found in the Clinical Pharmacology Analysis Plan (CPAP) .

Descriptive statistics (N, mean, SD, CV%, median, minimum and maximum) will be used to summarize the PK parameters for alogliptin and pioglitazone by regimen. In addition, geometric means will be computed for AUCs and C_{max} . The PK parameters of interest are listed in Table 2.

Box plots for both alogliptin and pioglitazone C_{max} and AUC_{72} will be generated by regimen and will be presented Regimen A versus Regimen B and Regimen C versus Regimen D.

Table 1 Collection of blood samples for PK analysis

| Analyte | Matrix | Dosing Day | Scheduled Time (hours) |
|--------------|--------|------------|---|
| Alogliptin | Plasma | 1 | Predose (within 15 minutes prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose |
| Pioglitazone | Plasma | 1 | Predose (within 15 minutes prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose |

Table 2 Pharmacokinetic Parameters

| Symbol/Term | Definition |
|-------------|---|
| AUC_{72} | Area under the concentration-time curve from the time 0 to time 72 hours. |
| AUC_t | Area under the concentration-time curve from time 0 to time t. |
| CCI | |
| 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_{max} | Time of first occurrence of C_{max} |

For each analyte, an analysis of variance (ANOVA) will be performed on natural logarithm transformed C_{max} and AUC_{72} with factors for sequence, the subject nested within sequence, period and regimen. The random effect subject nested within sequence will be the error term for testing the sequence effect. Other factors will be tested with the residual as the error term. For the relative bioavailability (BA) determination, pairwise comparisons will be performed to assess the relative BA of alogliptin and pioglitazone via point estimates and 90% confidence interval (CI) for the ratio of C_{max} and AUC_{72} central values for Regimen A (test) versus Regimen B (reference) as well as Regimen C (test) versus Regimen D (reference). CCI [REDACTED]

A conclusion of bioequivalence in the PK of each analyte between test regimen will be reached if the 90% CIs for C_{max} and AUC_{72} are within the (0.80-1.25) interval.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

All summaries and analyses of safety data are based on subjects in the Safety Analysis Set. Unless otherwise specified, the safety data will be summarized by study arm.

7.11.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) or serious adverse event (SAE) that started or worsened after first study drug administration and within 14 days (30 days if SAE) of last dose of study drug (onset date – date of last dose + 1 ≤ 14), see Protocol Section 10.2.1.1. 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 14 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. Any subject that doesn't not complete all 4 regimens/periods will be included in the AE summaries, and will be included in each of the regimens for which they

were treated and any AEs happening after their last regimen exposure (inclusive of 30 days) will be included in the tally of that regimen.

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 denominator, within a regimen summary, will be the total number of subjects that received the regimen.

The following TEAE tables will be summarized by part.

- Overview of TEAEs.
- TEAEs by SOC and PT.
- Most Frequent TEAEs by PT term
- Most Frequent Non-Serious TEAEs by PT
- Relationship of TEAEs to Study Drug by SOC and PT.
- Study 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 $\geq 5\%$ (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

Laboratory samples will be obtained following a minimum 8-hour overnight fast on Day 1 of Period 1 (pre-dose), and Day 4 of Period 4 (or Study Exit in case of early termination), see Appendix A. Baseline will be defined as the Day 1 value.

Laboratory values for hematology, serum chemistry, and urinalysis, see protocol section 9.1.8, will be summarized by regimen and by all subjects Overall. Individual subject values together with treatment sequence assignment will be presented in data listing; values that meet the Takeda predefined markedly abnormal value (MAV) criteria, [Appendix B](#), and/or outside normal range will be flagged in the data listing. For each laboratory parameter, where possible, the following will be performed:

- Descriptive statistics for change from baseline,

- Number and percentage of subjects with a value outside normal range,
- Number and percentage of subjects with a value meeting MAV criteria.

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 an MAV for a 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.

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. 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](#), including baseline and the final visit. The ECG evaluations will be categorized as Normal; Abnormal, not clinically significant; and Abnormal, clinically significant. ECG results will be presented as a shift from baseline table and all ECG data will be presented in data listings.

7.11.5 Other Observations Related to Safety

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

All cases of overdose will be listed.

Follow-up phone call information will be listed.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

Not applicable

Appendix A Study Procedures

| Study Day: | Days -28 to -2 (b) | Drug Intake Periods 1 through 4 (a) | | | | | Study Exit (Day 4 of Period 4)/ Early Termination Visit | Follow-up Phone Call (d) |
|---|--------------------------|-------------------------------------|--------------|-------|-------|---------------------------------------|--|--------------------------------|
| | | Day -1 (Check- in) | Day 1 (c) | Day 2 | Day 3 | Day 4 (Period s 1, 2, and 3) | | |
| Informed consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demographics and medical history | X | | | | | | | |
| Medication history | X | | | | | | | |
| Physical examination | X | X | | | | | X | |
| Vital signs (e) | X | X | X | | | X | X | |
| Height, weight and BMI | X | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X |
| 12-lead ECG (f) | X | X | | | | | X | |
| Clinical laboratory evaluations (g) | X | | X (h) | | | | X | |
| Urine drug, cotinine, and alcohol breath screen | X | X | | | X | X | X | |
| Urine pregnancy test (hCG) (i) | X | X | | | | | X | |
| HBsAg, Anti-HCV, HIV, and syphilis (i) | X | | | | | | | |
| Confinement | | X | X (j) | X (j) | | | | |
| Study drug dosing (k) | | | X | | | | | |
| PK blood collection (l) | | | X | X | X | X | X | |
| Predose/AE assessment (m) | X | X | X | X | X | X | X | X |

(a) There will be at least 7 days between the dose in 1 period and the dose in a subsequent period.

- (b) Screening may consist of 1 or more visits. Subjects will sign an informed consent form at the first visit and return to the clinic in a fasted state for safety laboratory testing at the second visit. Screening procedures must be performed within 28 days prior to administration of investigational product.
- (c) Day 1 of each drug intake period.
- (d) Follow-up phone call will be made 14 ± 2 days after study exit to inquire about any AE or SAEs, and concomitant medications taken since final dose. Any AE/SAE spontaneously reported within 30 days postdose will be included within the database as AEs.
- (e) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute). Vital signs will be measured just prior to dosing on Day 1 of periods 1 through 4. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.
- (f) ECG performed at Screening, Check-in (Day -1 of Period 1), and Study Exit Day 4 of Period 4, or if a subject terminates early from the study.
- (g) Hematology, serum chemistries, and urinalysis tests will be done at a local laboratory.
- (h) Predose hematology, serum chemistries, and urinalysis tests will be done for Period 1 only.
- (i) A urine pregnancy test and HBsAg, Anti-HCV, HIV, and syphilis tests will be done locally.
- (j) Following the 24-hour blood sample collection on Day 2 of each period, subjects will be discharged from the clinic and will return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures.
- (k) Study drug will be administered on Day 1 of each period at 08:00 (± 1) hours, following an 8- hour fast. Dosing may be staggered to help facilitate logistics at the site.
- (l) Blood samples for PK obtained predose (within 15 minutes prior to dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. The PK sample should not be collected at the Early Termination Visit if a PK collection is not scheduled.
- (m) Predose AEs 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 through to the follow-up phone call.

Appendix B Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

| Parameter | Unit | Low Abnormal | High Abnormal |
|----------------|--------------|--------------------------------|---------------------------------|
| Hemoglobin | Both | $< 0.8 \times \text{LLN}$ | $> 1.2 \times \text{ULN}$ |
| Hematocrit | Both | $< 0.8 \times \text{LLN}$ | $> 1.2 \times \text{ULN}$ |
| RBC count | Both | $< 0.8 \times \text{LLN}$ | $> 1.2 \times \text{ULN}$ |
| WBC count | Both | $< 0.5 \times \text{LLN}$ | $> 1.5 \times \text{ULN}$ |
| Platelet count | Conventional | $< 75 \times 10^3/\mu\text{L}$ | $> 600 \times 10^3/\mu\text{L}$ |
| | SI | $< 75 \times 10^9/\text{L}$ | $> 600 \times 10^9/\text{L}$ |

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 | -- | $> 3 \times \text{ULN}$ |
| AST | Both | -- | $> 3 \times \text{ULN}$ |
| Alkaline phosphatase | Both | -- | $> 3 \times \text{ULN}$ |
| Total bilirubin | Conventional | -- | $> 2.0 \text{ mg/dL}$ |
| | SI | -- | $> 34.2 \mu\text{mol/L}$ |
| GGT | Both | -- | $> 3 \times \text{ULN}$ |
| Albumin | Conventional | $< 2.5 \text{ g/dL}$ | -- |
| | SI | $< 25 \text{ g/L}$ | -- |
| Total protein | Both | $< 0.8 \times \text{LLN}$ | $> 1.2 \times \text{ULN}$ |
| Creatinine | Conventional | -- | $> 2.0 \text{ mg/dL}$ |
| | SI | -- | $> 177 \mu\text{mol/L}$ |
| Blood urea nitrogen | Conventional | -- | $> 30 \text{ mg/dL}$ |
| | SI | -- | $> 10.7 \text{ mmol/L}$ |
| Sodium | Conventional | $< 130 \text{ mEq/L}$ | $> 150 \text{ mEq/L}$ |
| | SI | $< 130 \text{ mmol/L}$ | $> 150 \text{ mmol/L}$ |
| Potassium | Conventional | $< 3.0 \text{ mEq/L}$ | $> 6.0 \text{ mEq/L}$ |
| | SI | $< 3.0 \text{ mmol/L}$ | $> 6.0 \text{ mmol/L}$ |
| CPK | Both | -- | $> 5 \times \text{ULN}$ |

ALT= alanine aminotransferase, AST= aspartate aminotransferase, GGT= γ -glutamyl transferase, CPK= creatine phosphokinase, 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 | °C | < 35.6 | >37.7 |

ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|-----------|--------------------------------|--|
| PPD | Statistical Approval | 20-Jun-2018 14:26 UTC |
| | Pharmacovigilance Approval | 20-Jun-2018 14:28 UTC |
| | Biostatistics Approval | 20-Jun-2018 14:40 UTC |
| | Clinical Pharmacology Approval | 27-Jun-2018 21:27 UTC |
| | Clinical Science Approval | 03-Jul-2018 19:48 UTC |