Official Title:	**Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC 67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs over a 6-Month Treatment Period**
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Otsuka

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug **OPC-67683 (Delamanid)**

Protocol No. 242-12-233

IND No. 76,728

Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC 67683) in Pediatric Multidrug resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs over a 6 Month Treatment Period

Investigational Medicinal Product
Delamanid (OPC-67683)

Statistical Analysis Plan

Version: Final
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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
ADAM	Analysis data model
ADSL	Subject-level analysis dataset
AE	Adverse event
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma-time concentration curve
AUC0-24	Area under the plasma-time concentration curve from time zero to 24 hours
BID	Dosing twice per day
BMI	Body mass index
BP	Blood pressure
CA	Competent authority
CDISC	Clinical Data Interchange Standards Consortium
CFU	Colony Forming Units
CI	Confidence interval
Cmax	Peak (maximal) concentration of drug in plasma/serum
CRO	Contract Research Organization
CSF	Cerebral Spinal Fluid
CYP	Cytochrome P-450
DILI	Drug Induced Liver Injury
DOTS	Directly-observed therapy short-course
DST	Drug susceptibility testing
DS-TB	Drug-susceptible tuberculosis
EB	Ethambutol
EBA	Early bactericidal activity
EC	Ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EFV	Efavirenz
EU	European Union
FDA	(United States) Food and Drug Administration
FOCBP	Female of child-bearing potential
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
IC	Inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification
IDM	Interval duration measurement
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INH	Isoniazid

INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
ISR	Immediate Safety Report
LMP	Last menstrual period
LPV	Lopinavir
LTBI	Latent TB infection
MedDRA	Medical Dictionary for Regulatory Activities
MD	Medical doctor
MDR-TB	Multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
NTBP	National Tuberculosis Program
OBR	Optimized background regimen
PD	Pharmacodynamic
P-gp	P-glycoprotein
PIP	Pediatric Investigational Plan
PK	Pharmacokinetics
PO	Oral route of administration
POPPK	Population pharmacokinetics
PT	Preferred term
PZA	Pyrazinamide
QD	Once daily
QTc	Corrected QT interval
QTcB	QTc corrected by Bazett formula
QTcF	QTc corrected by Fridericia formula
RR	Respiratory rate
RTV	Ritonavir
SAE	Serious adverse event
SCC	Sputum culture conversion
SD	Standard deviation
SMC	Safety Monitoring Committee
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TFV	tenofovir
t1/2	Elimination half-life
t1/2z	Terminal elimination half-life
TSH	Thyroid stimulating hormone
TST	Tuberculin skin test
ULN	Upper limit of normal
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant TB

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of safety, tolerability, pharmacokinetics (PK) and efficacy of Otsuka Pharmaceutical Development and Commercialization (Otsuka) Trial 242-12-233. All amendments to the protocol are taken into consideration in developing this SAP.

2 Study Objectives

2.1 Primary Objectives

- Safety and tolerability: To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB for the age-specific delamanid doses determined in Trial 232.
- Pharmacokinetics: To report delamanid and metabolite plasma concentrations at each visit by age groups and to conduct population pharmacokinetics (POPPK) anlaysis of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB.

2.2 Secondary objectives:

- To evaluate the pharmacokinetic (PK)/ pharmacodynamics (PD) relationship of delamanid and its metabolite DM-6705 plasma concentrations and change in QTc when delamanid is administered in combination with OBR during a 6-month treatment period in pediatric patients with MDR-TB.
- Efficacy: To evaluate the efficacy of delamanid when administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB.
- To determine the palatability of the delamanid pediatric formulation.

3 Study Design

This is a Phase 2, open-label, multi-dose, age de-escalation multicenter trial to assess the long-term safety, tolerability, PK, and efficacy of delamanid plus OBR over a 6-month treatment period in pediatric patients with MDR-TB who have successfully completed Trial 232. Since the trial is an extension of Trial 242-12-232 (Trial 232), patients must complete Trial 232 to roll-over to the current Trial 242-12-233 (Trial 233). Those patients who have completed Trial 232 and choose to enter Trial 233 must rollover from Trial 232 within 30 days after completing that Trial. If any patients terminate Trial 232 early or choose not to enter Trial 233, patients will be recruited to enter and complete Trial 232

first, and then rollover into Trial 233. However, patients who terminate Trial 233 early will not be replaced. Subject population is listed in Table 3-1 and study design schematic is illustrated in Figure 3-1.

Patients who enter Trial 233 will retain the same unique identification number and the same age group assigned to them in Trial 232:

Table 3-1 Subject Population

Group	Category	Sample Size (N)	Administration
1†	Age 12 -17 years	6+	Adult formulation of delamanid 100 mg BID + OBR for 6 months
2‡	Age 6 -11 years	6+	Adult formulation of delamanid 50 mg BID + OBR for 6 months
3‡	Age 3 -5 years	12+	Pediatric formulation of delamanid (DPF) 25 mg BID + OBR for 6 months
4‡	Age 0 -2 years	12+	Pediatric formulation of delamanid based on body weight + OBR: • Patient > 10 kg will receive DPF 10 mg BID + OBR • Patient > 8 and <= 10 kg will receive DPF 5 mg BID + OBR • Patient <= 8 kg will receive DPF 5 mg QD + OBR • Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12)

†: *Group 1 must include at least 2 but no more than 5 females.*

‡: *Group 2, 3, 4 must include both genders.*

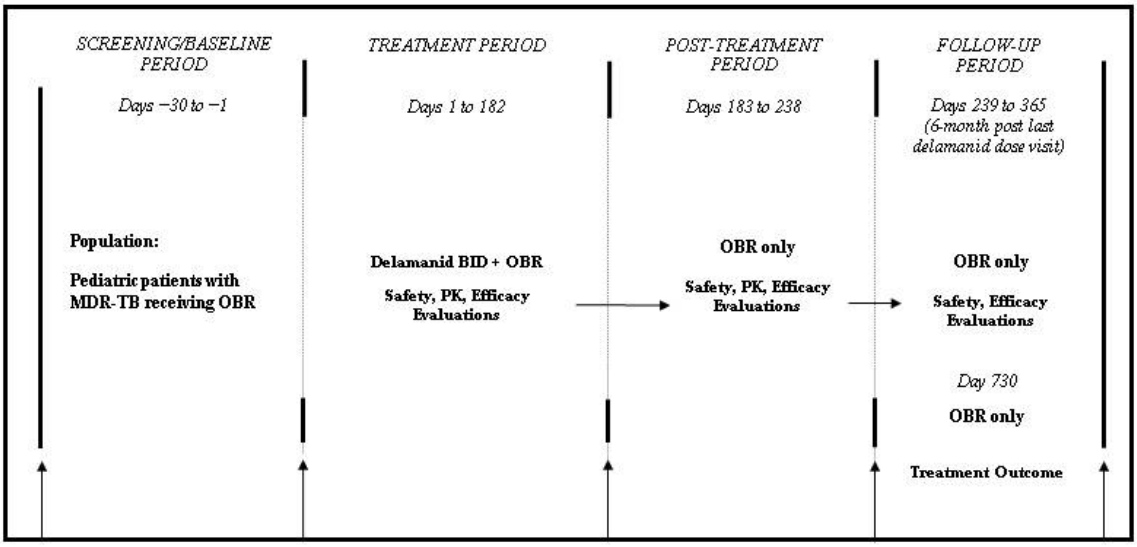

Figure 3-1 Trial Design Schematic

4 Sample Size and Power Justification

Since patients are rolled over directly from Trial 232, no power/sample size calculation was performed for this trial and no formal statistical hypothesis test is planned due to the small sample size. All statistical presentations will be descriptive.

5 Statistical Analysis

5.1 General Principles

All data processing, summarization and analyses will be performed using version of 9.4 or higher of SAS®-statistical software packages. Data will be presented in summary tables by age groups, and by study time points if applicable.

Without distinction, Descriptive Continuous Statistics will include the number of patients / observations (N), mean, standard deviation (SD), min and max by default; Descriptive Categorical Statistics will include frequency counts and percentages [n (%)]. The denominator for percentage calculations will be the total number of patients in the analysis sample, or the subset of the analysis sample if the analyses are restricted for the subset of the analysis sample only, as defined in section 5.2, unless specified otherwise. No formal statistical hypothesis testing will be performed.

When a measurement is repeated for the same visit, the last of repeat values will be used for production of summary tables. International System of Units (SI) will be applied for all analyses unless specified otherwise.

5.2 Datasets for Analysis

For safety and PK summaries, the following study samples are defined in Analysis Data Model [ADaM] subject-level analysis dataset [ADSL] and naming conventions will follow Clinical Data Interchange Standards Consortium [CDISC] standards.

- **Safety Sample**: comprises the patients who have received any amount of study medication in Trial 233, regardless of any protocol deviation or violation.
- **Efficacy Sample:** comprises all patients with at least one efficacy endpoint available, the efficacy end points include: 1) chest radiograph result; 2) investigator assessed clinical signs and symptoms of tuberculosis; 3) microbiologic assessment of sputum; 4) evaluable change from baseline in body weight or height at treatment period.

5.3 Definition of Baselines

Baseline is in general defined as the latest evaluation prior to the first dose in study 233, from both scheduled and unscheduled visits in either Trial 233, or Trial 232 if not applicable from Trial 233.

5.4 Handling of Missing Data

All analyses are performed on the observed data and no missing data imputation is needed.

5.5 Demographic and Baseline Characteristics

Baseline demographic characteristics including age, gender, race, ethnicity, height, height percentile for age, weight, weight percentile for age, body mass index (BMI) and menstruation will be summarized by age group for the Safety and Efficacy samples respectively using the baseline assessments. Descriptive statistics will be tabulated by age groups.

5.6 Medical History

General medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 (or a later version if updated during the study). All medical history will be listed, and Descriptive Categorical Statistics for patients with any medical history will be tabulated for safety sample by system organ class (SOC) and preferred term (PT) by age groups.

5.7 Primary Outcome Analysis

5.7.1 Safety Outcome Variables

Safety and Tolerability was assessed by adverse events (AEs), physical examination including visual and audiometry assessments, vital signs, electrocardiograms, clinical laboratory tests (serum chemistry, hematology, urinalysis and other laboratory tests), .

Safety parameters will be summarized by incidence rates and their change from baseline if applicable. Change from baseline is summarized for observed cases at each scheduled post-baseline visit and for the last visit.

5.7.1.1 Adverse Events

All adverse events (AEs) recorded will be classified by SOC and PT according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the time of analysis.

Treatment emergent AE (TEAE) is defined as any new adverse event experienced by a study subject that occurs after the initiation of (investigational) Medicinal Product ((I)MP) administration; an event or pre-existing medical problem that has changed adversely in nature or severity from baseline in a patient/subject while receiving (I)MP.

The seriousness of AEs is assessed as “Death”, “Life-threatening condition”, “Persistent or significant incapacity”, “Hospitalization- initial or prolonged”, “Congenital anomaly or birth defect”, “Medically significant condition” and “Non-serious”.

The severity of all AEs is recorded as “Mild”, “Moderate” and “Severe”.

The relationship between an AE and study drug is assessed as “Related”, “Possibly Related”, “Unlikely Related” and “Not Related”.

Action taken for AEs is recorded as “Drug Interrupted”, “Drug Withdrawn”, “Dose Not Changed”, “Not Applicable” and “Unknown”.

Adverse event outcome is assessed as “Recovered/Resolved”, “Recovering/Resolving”, “Recovered/Resolved with sequelae”, “Not recovered/Not resolved”, “Fatal” and “Unknown”.

The number and percentage of the TEAEs will be summarized overall by SOC (sorted alphabetically) and PT (sorted by descending overall total).

Patients with more than one AE within a particular SOC or PT are counted only once for that PT and the maximum severity will be selected. AEs with missing intensity/severity

will be included in the overall count of patients with AEs, but will not be included in the counts in summary for severity.

- Incidence of TEAEs
- Incidence of TEAEs by severity
- Incidence of potentially drug-related TEAEs (including 'related' and 'possibly related')
- Incidence of TEAEs with an outcome of death
- Incidence of treatment-emergent serious adverse events
- Incidence of drug-discontinuations (drug withdrawn) due to TEAEs
- Incidence of non-serious AEs [NSAE] with incidence rate 5% or higher by System Organ Class and MedDRA Preferred Term.

5.7.1.2 Clinical Laboratory Data

Data for the hematology, blood chemistry and urinalysis analytes received will be analyzed. The quantitative change in hematology, blood chemistry, and urinalysis analytes assessment results will be calculated relative to baseline. Laboratory tests with character results that cannot be quantitated by change from baseline will presented in tables with counts and percentages. Data obtained in the eCRF for additional analytes not required by the protocol will not be summarized, but will be included in listings.

Shift tables will be produced for assessing changes from baseline in clinical laboratory measurements using an ordinal scale (ie, low, normal, high based on lab normal range criteria).

Summary for frequency and percentage of laboratory tests that are newly occurred clinical significant during the study will be summarized for each laboratory parameter by age group. The clinical significant lab test result criteria is based on Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events[1]. Lab results with severity grade 3 or above is defined as clinical significant for this study and the criteria are listed in Appendix 1.

Listings of lab test results that are clinically significant will be presented.

A listing of all patients' lab result will be presented for each lab test and the values that are abnormal will be flagged as low (L) or high (H) in data listings.

If there are repeats for a certain lab test at a visit, then the last repeat value will be used in summaries. Post-baseline data from all unscheduled visits will not be included in the

summary tables by visits, but will be included in clinical notable change table and listings.

5.7.1.3 Drug Induced Liver Injury (DILI)

The potential DILI case will be presented in tables and listings:

- AST or ALT ≥ 3 x ULN and total bilirubin to >= 2 ULN

5.7.1.4 Physical Examination and Vital Signs

Vital signs will be listed and summarized by age groups and by visits:

- Weight (kg);
- Weight percentile for age.
- Height (cm);
- Height percentile for age
- Body temperature (°C);
- Heart rate (beats/min);
- Respiratory rate (breaths/minute);
- Systolic and diastolic blood pressure (mm Hg);
- BMI (kg/m2).

Physical examination [HEENT; Thorax; Abdomen; Urogenital; Extremities; Neurological; Skin and Mucosae] and vital signs data and changes from baseline in vital signs will be summarized by age group using Descriptive Continuous Statistics.

In addition, a listing of patients with at least one potentially clinically significant vital signs result will be presented for each vital sign parameter. Criteria for potentially clinically significant vital sign abnormalities are listed in Appendix 2. Summary for potentially clinically significant vital signs by visit, and newly acquired potentially clinically significant result during the treatment period will be presented for each vital sign by age group.

Post-baseline data from all unscheduled visits will not be included in the summary tables by visits, but will be included in clinical notable change table and listings.

5.7.1.5 Electrocardiogram Results

Continuous ECG parameters, including Heart rate, PR interval, QRS interval, QT intervals and QTc (including both QTcB and QTcF) will be summarized for:

- Descriptive Continuous Statistics on actual measurements and change from baseline.

- Summary table for patients with potentially clinically significant results. Criteria for potentially clinically significant vital sign abnormalities are listed in Appendix 3.
- Number and percentage of subjects with new qualitative abnormalities in rate, rhythm, conduction, morphology, including myocardial infarction, ST Segment, T Wave or U Wave abnormalities.
- Listing of patients with at least one potentially clinically significant ECG abnormalities result during the treatment period.

Data from all unscheduled visits will not be included in the summary tables for the changes from baseline by visits, but will be included in summary tables for the incidence of potentially clinically significant abnormalities and all listings.

5.7.1.6 Additional Safety Assessments

Visual and audiometry assessment results will be summarized and listed by study visits.

5.8 Extent of Exposure to Trial Medication

Number of days patients were exposed to IMP will be summarized by duration categories using counts and frequencies for the Safety Sample.

Duration of exposure to study drug will be defined as (date of last dose - date of first dose +1).

5.9 Treatment Compliance

Acceptability of delamanid will be summarized by visit by age group. And the dose administration of delamanid will be listed and DOT plan compliance is shown in the listing.

5.10 Protocol Deviation

Protocol deviations, as a measure of quality of study conduct, are summarized by type of deviation, and by age group for the safety sample, using Descriptive Categorical Statistics. Protocol deviations collected from CRF and generated from programmable cross-checks of data will be pooled together and listed by type of deviation, and by patient respectively. Nature of the violation, specified as either major or minor, will be included in the listing.

5.11 Pharmacokinetic Analysis of Plasma

Delamanid and metabolite plasma concentrations will be reported with descriptive statistics at each visit day per age group. In addition, delamanid data from this trial will

be combined with PK data from Trial 232 for a separate population PK analysis and report and will be conducted by Clinical Pharmacology group.

5.11.1 Pharmacokinetic Assessment of Cerebral Spinal Fluid (CSF)

In patients where a lumbar puncture is clinically indicated during the routine management of a child enrolled in the trial, CSF concentrations of delamanid will be measured and reported. The delamanid CSF concentration will be listed by patient together with the timing of the lumbar puncture in relation to the timing of the dose. If adequate data is available, the concentrations will be summarized using descriptive statistics.

5.12 Secondary Outcome Analysis

5.12.1 Pharmacokinetics/Phamacodynamics

PK/PD analysis will be performed by Clinical Pharmacology group to determine the relationship of delamanid and DM-6705 plasma concentrationsto any changes in QTc interval.

5.12.2 Efficacy Outcome Analysis

Descriptive Categorical Statistic will be summarized for each efficacy endpoint and presented in listings by patient, no formal statistical inference performed.

- Chest radiography results;
- Body weight/height
- Investigator-assessed signs and symptoms of tuberculosis:
  1) Cough;
  2) Fever;
  3) Weight loss;
  4) Failure to thrive;
  5) Hemoptysis;
  6) Dyspnea;
  7) Chest pain;
  8) Night sweats;
  9) Loss of appetite;

- Sputum culture conversion (SCC) will be assessed in patients with culture-positive and able to produce sputum or provide other biological specimens or with investigator order for purpose of routine management of the patient;

5.12.3 Palatibility

The palatability of the pediatric formulation will be assessed using an age-appropriate visual hedonic scale and clinical assessment (Group 3 and 4 only). The counts and percentages will be tabulated in frequency tables.

5.12.4 Final Treatment Outcomes Assessed by the Principal Investigator

Final treatment outcomes will be assessed by the investigator at 24 months of initial IMP dose, according to the WHO outcome definitions for treating patients with MDR TB. Treatment outcome (Cured, Treatment Completed, Died, Treatment Failed, Lost to follow-up, Not evaluated) will be provided by treatment group. Frequency and percentage of patients achieving a favorable treatment outcome (cured or treatment completed) will be summarized by age group, using descriptive categorical statistics. Listing of treatment outcome will also be provided by age group.

5.13 Concomitant Medications

Medications received concomitantly with study drug will be collected in the database and coded using the most recent WHO Drug Dictionary , Anatomical Therapeutic Chemical (ATC) Classification codes.

Descriptive Categorical Statistics will be tabulated by drug classification according to age group for the following periods:

- Prior to taking trial therapy;
- During the trial therapy;
- During the scheduled follow-up period after trial therapy complete.

5.14 Patient Disposition, Completion Rate and Reasons for Discontinuation

The number and percentage of patients who complete the trial and who discontinue early, including a breakdown of the primary reasons for discontinuation, will be summarized using Descriptive Categorical Statistics. Patients who are evaluated at the last scheduled visit of the trial, the follow-up visit (Visit 19, Day 365), will be defined as trial completers. The discontinuation by primary reasons will be summarized by age group for Enrolled and PK samples.

5.15 Discontinuation

A patient disposition table will be presented including the following categories:

Safety (Treated)
Efficacy
PK
Early discontinued
Completed study treatment

The number and percentage of patients who complete the trial and who discontinue early, including a breakdown of the primary reasons for discontinuation, will be summarized using Descriptive Categorical Statistics. The discontinuation by primary reasons will be summarized by age group for Enrolled and PK samples:

Lost to follow-up

Adverse events

Sponsor discontinued study

Subject met withdrawal criteria

Subject was withdrawn from participation by the investigator

Subject withdrew consent to participate

Protocol deviation

5.16 Interim Analysis

Safety, tolerability, PK, and efficacy of delamanid in children 6 to 17 years of age will be reviewed when a full complete data is available.

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7 Bibliography

1 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1. July 2017

Appendix 1 Serum Chemistry, Hematology and Urinalysis Lab Test Results Clinical Significant Criteria Based on Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

LAB GROUP	TEST	UNITS	SEX	AGE Group	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Chemistry	Albumin, Low	g/dL	Male/Female	All	< 2.0	NA
Chemistry	Albumin, Low	g/L	Male/Female	All	< 20	NA
Chemistry	Alkaline Phosphatase, High		Male/Female	All	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Chemistry	ALT or SGPT, High		Male/Female	All	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Chemistry	AST or SGOT, High		Male/Female	All	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Chemistry	Total Bilirubin, High		Male/Female	> 28 days of age	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Chemistry	Calcium, High	mg/dL	Male/Female	≥ 7 days of age	12.5 to < 13.5	≥ 13.5
Chemistry	Calcium, High	mmol/L	Male/Female	≥ 7 days of age	3.13 to < 3.38	≥ 3.38
Chemistry	Calcium, Low	mg/dL	Male/Female	≥ 7 days of age	6.1 to < 7.0	< 6.1
Chemistry	Calcium, Low	mmol/L	Male/Female	≥ 7 days of age	1.53 to < 1.75	< 1.53
Chemistry	Creatinine, High		Male/Female	All	> 1.8 to < 3.5 x ULN	≥ 3.5 x ULN
Chemistry	Glucose, High	mg/dL	Male/Female	All	> 250 to 500	≥ 500
Chemistry	Glucose, High	mmol/L	Male/Female	All	13.89 to < 27.75	≥ 27.75
Chemistry	Glucose, Low	mg/dL	Male/Female	≥ 1 month of age	30 to < 40	< 30
Chemistry	Glucose, Low	mmol/L	Male/Female	≥ 1 month of age	1.67 to < 2.22	< 1.67
Chemistry	Cholesterol, High	mg/dL	Male/Female	All	≥ 300	NA
Chemistry	Cholesterol, High	mmol/L	Male/Female	All	≥ 7.77	NA
Chemistry	Inorganic Phosphorus, Low	mg/dL	Male/Female	> 14 years of age	1.0 to < 1.4	< 1.0
Chemistry	Inorganic Phosphorus, Low	mmol/L	Male/Female	> 14 years of age	0.32 to < 0.45	< 0.32
Chemistry	Inorganic Phosphorus, Low	mg/dL	Male/Female	<1 to 14 years of age	1.5 to < 2.5	< 1.5
Chemistry	Inorganic Phosphorus, Low	mmol/L	Male/Female	<1 to 14 years of age	0.48 to < 0.81	< 0.48
Chemistry	Magnesium, Low	mEq/L	Male/Female	All	0.6 to < 0.9	< 0.6
Chemistry	Magnesium, Low	mmol/L	Male/Female	All	0.30 to < 0.45	< 0.30
Chemistry	Potassium, High	mEq/L	Male/Female	All	6.5 to < 7.0	≥ 7.0
Chemistry	Potassium, High	mmol/L	Male/Female	All	6.5 to < 7.0	≥ 7.0

LAB GROUP	TEST	UNITS	SEX	AGE Group	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Chemistry	Potassium, Low	mEq/L	Male/Female	All	2.0 to < 2.5	< 2.0
Chemistry	Potassium, Low	mmol/L	Male/Female	All	2.0 to < 2.5	< 2.0
Chemistry	Sodium, High	mEq/L	Male/Female	All	154 to < 160	≥ 160
Chemistry	Sodium, High	mmol/L	Male/Female	All	154 to < 160	≥ 160
Chemistry	Sodium, Low	mEq/L	Male/Female	All	121 to < 125	≤ 120
Chemistry	Sodium, Low	mmol/L	Male/Female	All	121 to < 125	≤ 120
Chemistry	Triglycerides, High	mg/dL	Male/Female	All	>500 to < 1,000	> 1,000
Chemistry	Triglycerides, High	mmol/L	Male/Female	All	>5.7 to 11.4	> 11.4
Chemistry	Uric Acid, High	mg/dL	Male/Female	All	12.0 to < 15.0	≥ 15.0
Chemistry	Uric Acid, High	mmol/L	Male/Female	All	0.71 to < 0.89	≥ 0.89
Hematology	Activated Partial Thromboplastin Time, High		Male/Female	All	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Hematology	Absolute CD4+ Count, Low	cell/mm^3	Male/Female	All> 5 years of age (not HIV infected)	100 to < 200	< 100
Hematology	Absolute CD4+ Count, Low	cells/L	Male/Female	> 5 years of age (not HIV infected)	100 to < 200	< 100
Hematology	Absolute Lymphocytes, Low	cell/mm^3	Male/Female	> 5 years of age (not HIV infected)	350 to < 500	< 350
Hematology	Absolute Lymphocytes, Low	cells/L	Male/Female	> 5 years of age (not HIV infected)	0.350 x 10^9 to < 0.500 x 10^9	< 0.350 x 10^9
Hematology	Absolute Neutrophil Count, Low	cell/mm^3	Male/Female	> 7 days of age	400 to 599	<400
Hematology	Absolute Neutrophil Count, Low	cells/L	Male/Female	> 7 days of age	0.400 x 10^9 to < 0.599 x 10^9	< 0.400 x 10^9
Hematology	Hemoglobin, Low	g/dL	Male	≥ 13 years of age	7.0 to < 9.0	< 7.0
Hematology	Hemoglobin, Low	mmol/L	Male	≥ 13 years of age	4.34 to < 5.57	< 4.34
Hematology	Hemoglobin, Low	g/dL	Female	≥ 13 years of age	6.5 to < 8.5	< 6.5
Hematology	Hemoglobin, Low	mmol/L	Female	≥ 13 years of age	4.03 to < 5.25	< 4.03
Hematology	Hemoglobin, Low	g/dL	Male/Female	57 days of age to < 13 years of age	6.5 to < 8.5	< 6.5
Hematology	Hemoglobin, Low	mmol/L	Male/Female	57 days of age to < 13 years of age	4.03 to < 5.25	< 4.03
Hematology	Platelet Count, Decreased	cells/mm^3	Male/Female	All	25,000 to < 50,000	< 25,000
Hematology	Platelet Count, Decreased	cells/L	Male/Female	All	25.000 x 10^9 to < 50.000 x 10^9	< 25.000 x 10^9
Hematology	Prothrombin Time, High		Male/Female	All	1.50 to < 3.00 x ULN	≥ 3.00 x ULN

LAB GROUP	TEST	UNITS	SEX	AGE Group	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hematology	Partial Thromboplastin Time, High		Male/Female	All	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Hematology	White Blood Cell, Decreased	cells/mm^3	Male/Female	> 7 days of age	1,000 to 1,499	< 1,000
Hematology	White Blood Cell, Decreased	cells/L	Male/Female	> 7 days of age	1.000 x 10^9 to 1.499 x 10^9	< 1.000 x 10^9
Urinalysis	Urine Glucose		Male/Female	All	> 2+ or >500 mg	NA
Urinalysis	Urine Blood		Male/Female	All	Gross OR Presence of RBC casts OR Intervention indicated	Life-threatening consequences
Urinalysis	Urine Protein		Male/Female	All	3+ or higher	NA

RBC = red blood cell; ULN=upper normal limit

Appendix 2 Criteria for Potentially Clinical Significant Vital Sign Abnormalities

Variable	Change Relative to Baseline
Weight	Decrease of >=5% in body weight Increase of >=5% in body weight

Note: In order to be identified as "potentially clinical significant abnormal," an on-drug value must represent a change from the patient's baseline value of at least the magnitude shown in the "Change Relative to Baseline column.

Appendix 3 Criteria for Potentially Clinical Significant ECG Abnormalities

Classification	Criterion Value	Change Relative to Baseline
HR Outliers	< 50 bpm	Decrease of >= 25%
	> 100 bpm	Increase of >= 25%
PR Outliers	> 200 msec	Increase of >= 25%
QRS Outliers	> 100 msec	Increase of >= 25%
QT	New Onset (> 500 msec) §	
QTcB	New Onset (> 450 msec) § New Onset (> 480 msec) § New Onset (> 500 msec) §	Increase of >= 30 msec and <=60 msec Increase of >60 msec
QTcF	New Onset (> 450 msec) § New Onset (> 480 msec) § New Onset (> 500 msec) §	Increase of >= 30 msec and <=60 msec Increase of > 60 msec
U Waves	New Abnormal U Waves	
ST Segment	New ST Segment Changes	
T Waves	New T Wave Changes	
Rhythm	New Abnormal Rhythm	
Conduction	New Conduction Abnormality	

Note: In order to be identified as "potentially clinical significant abnormal," an on-drug value must meet the "Criterion Value" and also represent a change from the patient's pretreatment value of at least the magnitude shown in the "Change Relative to Baseline column.

§ New Onset is defined as "not present on baseline ECG but present on on-treatment ECG". New Onset (> 450 msec), or New Onset (> 480 msec), or New Onset (> 500 msec) means a patient who attains a value >450 msec, or >480 msec, >500 msec respectively during treatment period but not at baseline visit.

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