Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational New Drug Quabodepistat (OPC-167832)

Protocol No. 323-201-00007
IND No. 129303

A Phase 1, Single-center, Two-part, Open-label, Pharmacokinetic Trial to Assess the Potential for Cytochrome P450 3A Mediated Drug-drug Interactions with Orally Administered Quabodepistat (OPC-167832) Tablets in Healthy Adult Subjects

A Study to Test the Effects of Itraconazole and Carbamazepine on OPC-167832 in Healthy Men and Women

Statistical Analysis Plan
Phase 1
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity
AUC_t	Area under the concentration-time curve calculated to the last observableconcentration at time t
BID	Dosing twice per day
CI	Confidence interval
CL/F	Total body clearance of drug from plasma following extravascular administration
C_{max}	Peak (maximal) concentration of drug in plasma
eCRF	Electronic Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Early termination
FDA	(United States) Food and Drug Administration
HR	Heart rate
ICF	Informed consent form
IMP	Investigational medicinal product
IND	Investigational new drug
LLN	Lower limit of normal
LTFU	Lost to Follow-up
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	**Definition**
mg	Milligrams
mL	Milliliter
OPC	Otsuka Pharmaceutical Co.
PK	Pharmacokinetic(s)
PR	part of an ECG wave pattern (from P to R)
QRS	part of an ECG wave pattern (from Q to R to S)
QT	part of an ECG wave pattern (from QRS to T)
QTcB	QT Interval Bazett's formula
QTcF	QT Interval Fredericia's formula
RBC	Red blood cell
RR	inter-beat interval
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
ULN	Upper limit of normal

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for reporting of pharmacokinetics and safety data of Trial 323-201-00007. This is an open-label trial and no blinding/unblinding processes are used in this trial.

2 Trial Objectives

The primary objectives are: to assess the potential for CYP-mediated drug-drug interactions with OPC-167832:

- Inhibition of OPC-167832 metabolism via CYP3A by itraconazole.
- Induction of OPC-167832 metabolism via CYP3A by carbamazepine.

The secondary objectives are: to assess the safety and tolerability of OPC-167832 administered alone or in combination with itraconazole or carbamazepine

3 Trial Design

This is a single-center, 2-part, open-label, non-randomized single arm, drug-drug interaction (DDI) trial in healthy adult subjects. Part 1 (OPC-167832, itraconazole) and Part 2 (OPC-167832, carbamazepine) will have fixed sequence designs with 12 subjects in each part for a total of 24 subjects enrolled.

3.1 Type/Design of Trial

Following a screening period of up to 28 days, eligible subjects will enter the clinic (check-in) on the day prior to the first treatment day (Day −1).

For Part 1, the impact of CYP3A inhibition on the PK of OPC-167832 will be assessed. Subjects will receive a single, 30 mg, oral dose of OPC-167832 CCI in the fasted state on Day 1 with blood collections for PK assessment of OPC-167832 from Day 1 through Day 8. On Day 8, subjects will receive 200 mg doses of itraconazole in the morning and evening (200 mg twice daily [BID]) followed by 200 mg of itraconazole administered once daily on Day 9 through Day 14 to approach steady-state conditions for itraconazole. On Day 15, a single, 30 mg, oral dose of OPC-167832 CCI will be administered concurrently with a 200 mg dose of itraconazole in the fasted state with blood collections for PK assessment of OPC-167832 from Day 15 through Day 26. Once daily 200 mg doses of itraconazole will continue to be administered on Day 16 through Day 25. Subjects will be discharged from the clinic after the PK sample on Day 26 or early termination (ET).

For Part 2, the impact of CYP3A induction on the PK of OPC-167832 will be assessed. Subjects will receive a single, 30 mg, oral dose of OPC-167832 [redacted] on Day 1 in the fasted state with blood collections for PK assessment of OPC-167832 from Day 1 through Day 8. On Day 8 through Day 10, subjects will receive 100 mg BID carbamazepine followed by 200 mg BID carbamazepine administration on Day 11 through Day 13 and 300 mg BID carbamazepine administration on Day 14 through Day 31. On Day 25, a 30 mg oral dose of OPC-167832 [redacted] will be administered concurrently with the morning 300 mg dose of carbamazepine in the fasted state with blood collections for PK assessment of OPC-167832 from Day 25 through Day 32. Subjects will be discharged from the clinic after the PK sample on Day 32 or ET.

All subjects will be contacted by phone 30 days after the last dose of OPC-167832 to assess any new or ongoing AEs and to record concomitant medications.

3.2 Trial Treatments

OPC-167832, itraconazole, and carbamazepine will be administered orally to subjects as per the dosing schedule below. OPC-167832 [redacted] will be provided as 30 mg tablets, itraconazole will be administered as a 10 mg/mL oral solution, carbamazepine will be administered as the least number of tablets based on commercially available extended-release tablets (ie, 100 mg tablet, 200 mg tablet). Lower dose strengths of carbamazepine can be combined, ie, a 100 mg tablet and a 200 mg tablet should be combined to dose at 300 mg. All doses will be administered with approximately 240 mL of room temperature, still water. When itraconazole is administered, some of the 240 mL of water should be used to rinse the dosing container. All doses of OPC-167832 (administered on Days 1 and 15 in Part 1 and Days 1 and 25 in Part 2) will be administered following an overnight fast of at least 10 hours.

For Part 1, OPC-167832 and itraconazole will be administered in the morning at the same time each day. The BID dose of itraconazole on Day 8 will be administered every 12 hours (q12h). On days of serial PK sampling days (Days 1 and 15), subjects will be required to continue to fast from food for at least 4 hours following dosing of OPC-167832 and water will be restricted for 1 hour before to 2 hours after dosing of OPC-167832. Water is permitted ad libitum on all other days.

For Part 2, OPC-167832 and carbamazepine will be administered in the mornings at the same time each day and BID doses of carbamazepine will be administered q12h and at same time each evening. On days of serial PK sampling days (Days 1 and 25), subjects will be required to continue to fast from food for at least 4 hours following dosing of

OPC-167832 and water will be restricted for 1 hour before to 2 hours after dosing of OPC-167832. Water is permitted ad libitum on all other days.

Table 3.2-1 Dosing Schedule

Study Day	Time	Dose
PART 1		
1	morning	30 mg OPC-167832
8	morning	200 mg itraconazole
	evening	200 mg itraconazole
9 through 14	morning	Once-daily 200 mg itraconazole
15	morning	30 mg OPC-167832 and 200 mg itraconazole
16 through 25	morning	Once-daily 200 mg itraconazole
PART 2		
1	morning	30 mg OPC-167832
8 through 10	morning	100 mg carbamazepine extended release
	evening	100 mg carbamazepine extended release
11 through 13	morning	200 mg carbamazepine extended release
	evening	200 mg carbamazepine extended release
14 through 24	morning	300 mg carbamazepine extended release
	evening	300 mg carbamazepine extended release
25	morning	30 mg OPC-167832 and 300 mg carbamazepine extended release
	evening	300 mg carbamazepine extended release
26 through 31	morning	300 mg carbamazepine extended release
	evening	300 mg carbamazepine extended release

4 Trial Population

Twenty-four subjects in total will be enrolled in the trial, with 12 subjects enrolled in each part, such that approximately 10 healthy male or female subjects, 18 to 55 years of age, inclusive, complete each part of the trial. Discontinued subjects may be replaced at the discretion of the sponsor.

5 Sample Size

Sample size was selected assuming an intra-subject coefficient of variation for AUC of 25%, such that the point estimate of the ratio of geometric means for the PK parameters of OPC-167832 with and without coadministration of the perpetrator (itraconazole or carbamazepine) will fall within 83% and 120% of the true value with 90% confidence. Twenty-four subjects will be enrolled, 12 subjects in each part, to target approximately 10 healthy male or female subjects complete each trial part. (For definition of completer, see Section 6.6).

6 Statistical Analysis Sets

6.1 Efficacy Analysis Set

There are no efficacy analyses in this trial.

6.2 All Participants

All Participants includes all signatories of the informed consent form (ICF).

6.3 Enrolled Analysis Set

The enrolled analysis dataset includes all subjects that sign the informed consent form (ICF), and meet all eligibility criteria.

6.4 Safety Analysis Set

The safety dataset will include all enrolled subjects who have taken at least one dose of IMP.

In Part 1 of this trial, Investigational Medicinal Product (IMP) refers to OPC-167832 and/or itraconazole, and in Part 2 of this trial, IMP refers to OPC-167832 and/or carbamazepine.

6.5 Pharmacokinetic (PK) Analysis Set

The Pharmacokinetic (PK) analysis set will include all subjects who received at least one dose of IMP, and have at least one post-dose evaluable plasma concentration.

6.6 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and secondary objectives of the trial irrespective of whether or not the subject actually takes all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects in Part 1 who complete the last scheduled PK assessment on Day 26 and subjects in Part 2 who complete the last scheduled PK assessment on Day 32 will be defined as trial completers.

6.7 Definition of Baseline

In both parts 1 and 2, baseline will be the last available value prior to the start of IMP treatment.

For clinical laboratory data, see Section 10.3. For vital sign measurements, see Section 10.4. For ECGs, please see Section 10.6. For C-SSRS, see Section 10.7.

6.8 Handling of Missing Data

No data imputation will be performed for missing PK and safety data in this trial. The handling of concentrations below the lower limit of quantification will be according to the sponsor's data handling processes for PK data.

6.8.1 Incomplete Dates

Unless otherwise stated in the analysis sections (eg, AE and concomitant medication), the general rule for imputing incomplete dates when the year is present is to use January if only the month is missing and the first day of a month if only the day is missing, provided these dates are consistent with existing dates within the data and are chronologically consistent. If both month and day are missing, but the year is available, 01 Jan is imputed. If the year is unknown, the date will be considered as missing.

7 Primary and Secondary Outcome Variables

7.1 Primary Outcome Variables

The primary endpoints of the trial are the following PK parameters:

- maximum plasma concentration of the drug (C_{max})
- area under the concentration-time curve calculated to the last observable concentration at time t (AUC_t)
- area under the concentration-time curve from time zero to infinity (AUC_∞)

The effect of itraconazole or carbamazepine administration on the single-dose PK of OPC-167832 will be assessed using the above PK parameters in the presence and absence of either itraconazole (Part 1) or carbamazepine (Part 2).

7.2 Secondary Outcome Variables

Safety outcome variables for individuals will be based on

- Adverse Events
- Vital Signs and Physical Examination
- Electrocardiograms (ECGs)
- Clinical laboratory tests
- Columbia-Suicide Severity Rating Scale (C-SSRS) (for Part 2 only)

8 Disposition and Demographic Analysis

8.1 Subject Disposition

The number of subjects enrolled, the number of subjects who are treated, and the number of subjects who discontinue from the trial, together with the reasons for discontinuation taken from the eCRF status page, the number of completers and the number of subjects lost to follow-up, will be provided for each Part separately.

8.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all enrolled subjects by Part. Continuous variables (age, weight, and height) will be summarized by descriptive statistics: number of non-missing values, mean, median, standard deviation, minimum, and maximum. Categorical variables (sex, race, ethnicity, and gender) will be summarized by counts and percentages within each category. Demographic and baseline characteristics will be summarized for each Part separately.

8.3 Medical History

Listings for general medical history (coded using Medical Dictionary for Regulatory Activities [MedDRA] Version 25 or a later version, if available) based on safety analysis set will be provided for each Part.

8.4 Treatment Compliance

The date, time and dose of IMP administration during the trial will be recorded on the eCRF. Information regarding any inappropriately administered doses will also be documented on the eCRF. All doses of IMP will be administered while the subjects are in the clinic; compliance will be ensured by a mouth check during the oral dosing administration of IMP.

A listing of treatment compliance (dose administered) for each subject based on the safety analysis set will be provided for each Part.

8.5 Prior and Concomitant Medication

The investigator will record all medications (including prescription medications, over-the-counter medications, herbal remedies, vitamins and supplements, etc) and therapies taken by the subject from 30 days prior to first dose of IMP through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an

AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

Medications taken other than IMP will be coded using the WHO drug dictionary (WHODrug 3BG, 01 Mar 2022 or later version) and will be presented separately for each Part.

The proportion of subjects taking concomitant medications will be tabulated for the safety analysis set in the periods prior to, during and after the trial medication.

In addition, listings of concomitant mediations will be provided.

8.6 Prohibited Medications or Therapies

The use of prescription, over-the-counter, herbal medications, or vitamin supplements within 14 days prior to the first dose and during the treatment period of the trial are prohibited. Antibiotics or dietary supplements (eg, creatine) within 30 days prior to the first dose and during the treatment period of the trial are prohibited. Medications other than the protocol-specific trial interventions and the contraception specified in Appendix 10.3 are not to be taken during the trial; however, the sponsor may allow exceptions only if the medication is unlikely to affect the PK result.

A listing of prohibited medications taken during the trial will be provided.

8.7 Lost to Follow-up

Subjects who do not complete the last scheduled PK assessment on Day 26 for Part 1 and Day 32 for Part 2 during the trial intervention period, who do not have a known reason for discontinuation (eg, withdrew consent/assent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up."

Number of subjects lost to follow-up (LTFU) will be tabulated in the Subject Disposition table.

8.8 Protocol Deviations

Major protocol deviations, as recorded in the eCRF, will be listed.

9 Efficacy Analyses

Not applicable

10 Safety Analyses

The safety analysis will be conducted on the safety analysis set for each part separately. Safety variables to be analyzed include AEs, clinical laboratory assessments, vital signs,

12-lead ECGs, physical examinations, and the Columbia-Suicide Severity Rating Scale ([C-SSRS] Part 2 only). Descriptive statistics will be provided for the safety variables. Baseline measurements of safety variables are defined as the last measurement prior to the first dosing of IMP (also see Section 6.7).

10.1 Extent of Exposure

Extent of exposure to the trial medication for Safety Analysis Set will be summarized using descriptive statistics.

10.2 Adverse Events

All AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA, Version 25 or a later version if available).

Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the start of IMP treatment. TEAEs are all AEs which started after the start of IMP treatment; or if the event was continuous from baseline and worsens either in intensity or frequency, becomes serious, is assessed as IMP-related or results in death.

Relatedness of AEs to IMP will be collected for each IMP, individually, OPC 167832 and itraconozole for Part 1 and OPC 167832 and carbamazepine for Part 2.

A Serious Adverse Event (SAE) includes any event that results in any of the following outcomes:

- Death.
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.

  Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE and should be recorded as medical history.
- Congenital anomaly/birth defect.

- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

The frequency and percentage of subjects with the following events, together with the number of events, (events listed below), will be summarized by SOC, MedDRA preferred term, severity, and treatment for each of Part 1 and Part 2 separately

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- All AEs
- All SAEs
- TEAEs related to OPC-167832
- TEAEs related to Itraconazole
- TEAEs related to Carbamazepine
- TEAEs with an outcome of death
- Serious TEAEs
- Serious Related TEAEs
- AEs and TEAEs with a DAIDS grade >= 3 or severe events
- TEAEs leading to discontinuations of the IMP
- Non-serious TEAEs

Severity of AEs is graded by the Division of AIDS (DAIDS)[1] grading criteria. All AEs will be presented in a listing for each Part separately. Listings of death due to AEs, serious AEs, and AEs leading to discontinuation of the IMP (with specification of relatedness to specific IMP) will also be provided. A summary table of AEs will be presented for each part separately, containing the number and percentage of subjects experiencing the different categories of AEs, along with the number of AEs reported within each category.

10.3 Clinical Laboratory Data

Summary statistics for the clinical laboratory parameters at baseline, post-dose time points, and mean changes from baseline will be presented. The incidence of potentially clinically significant laboratory test abnormalities will be summarized for each test. Investigator assessment of clinical significance will be listed for abnormal assessments.

Criteria for the potentially clinically relevant laboratory test abnormalities are provided in Appendix 2.

In addition, the DAIDS Adverse Event Grading Tables will be used for identifying laboratory values of potential clinical relevance (Appendix 1).

According to FDA Guidance, laboratory measurements that signal the potential for drug-induced liver injury (DILI) will be reported. An incidence table and a listing will be provided for subjects who meet the criteria for potential serious hepatotoxicity will be provided (see Section 10.8).

Scheduled assessments will be summarized in tables. Unscheduled assessments will only appear in listings and in presentations for potentially clinically laboratory test abnormalities. If a test is identified as a repeat test, the repeat test value will replace the original value.

Baseline values are Day −1 values, or, if Day −1 values are not available, then baseline values will be the values collected during the screening period.

10.4 Vital Sign Data

Vital signs are measured at screening, on Day −1, pre-dose on Day 1. Baseline values will be predose values taken prior to first IMP treatment on Day 1. If multiple pre-dose Day 1 values are recorded, the chronologically last recorded value prior to first IMP treatment on Day 1 will be taken to be the baseline value. If there are no pre-dose Day 1 values, then baseline values will be taken to be the last value recorded on Day −1; if Day −1 values are missing, then the last screening value will be taken to be the baseline value.

Descriptive statistics will be provided for change from baseline in vital signs parameters. Incidence of treatment-emergent potentially clinically significant vital sign results will also be summarized. Listings of potentially clinically significant abnormalities will also be provided. If vital sign assessments are repeated for the same visit, the last repeat values will be used for production of mean change from baseline. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit identification. Criteria for Identifying Vital Signs of Potential Clinical Relevance are provided in Appendices 2 and 3.

10.5 Physical Examination Data

Physical examination (PE) findings will be listed by subject. PE findings marked as clinically significant (CS) will be flagged in the listings.

10.6 Electrocardiogram Data

Electrocardiogram measurements (will include HR, PR, QRS, RR, QT, QTcF, QTcB) and mean changes from baseline will be summarized by part and time point. The incidence of potentially clinically significant changes and abnormalities in ECG evaluations will be summarized. Electrocardiogram data will be presented in listings. In ECG listings, abnormal will also indicate whether CS or not. For ECG assessments, baseline is defined as the average of triplicate (if not collected as triplicate, then single, or duplicate values will be averaged) ECG values collected at check-in for each Part. If there are two or more sets of ECG (check-in) evaluations prior to first IMP dosing, the last set of triplicate (or duplicate or single, as applicable) will be averaged for presenting as the baseline values (whether these are scheduled or unscheduled). Predose ECGs will be reported as predose and are not part of the baseline assessments.

If the baseline value is missing, it will not be imputed.

ECG parameter values will be reported as received in the raw data. ECG data will be reported out in listings, with the actual value and change-from-baseline value included in the listing.

Averaged ECG parameters will be rounded down to the nearest integer for easy interpretability.

10.7 Suicidality Monitoring

Suicidality monitoring will be conducted only in subjects enrolled in Part 2 and at the time points described in the SoA (Table 1.3-2 of the protocol).

The “Baseline/Screening” version of the C-SSRS will be completed at screening. This will be the baseline assessment for the C-SSRS.

The “Since Last Visit” version will be completed at all other specified visits (including ET, if applicable).

The “Baseline/Screening” version be used to assess Suicidal Ideation and Suicidal Behavior in both the subjects' lifetime and within the past 12 months prior to screening. There are a maximum of 19 items to be completed: 7 required, 10 potential additional items if there is a positive response to a required item, and 2 items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

The C-SSRS data will be analyzed for evidence of any treatment-emergent issues related to suicidal ideation or behavior. The incidence of suicidality, suicidal behavior, and

suicidal ideation will be summarized by treatment group and visit. No inferential statistical analyses will be performed. C-SSRS data will be listed.

10.8 Potential Serious Hepatotoxicity

According to FDA Guidance, laboratory measurements that signal the potential for drug-induced liver injury (DILI) will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of following criteria:

1) ALT or AST ≥ 3 × upper limit of normal (ULN) (or baseline value for subjects with abnormal baseline)
2) increase in bilirubin ≥ 2 × ULN (or baseline value for subjects with abnormal baseline)

10.9 Other Safety Data

Not applicable.

11 Pharmacokinetic Analyses

OPC-167832 plasma concentrations will be listed by subject and summarized using descriptive statistics (N, mean, median, standard deviation, percentage coefficient of variation, minimum, and maximum) by treatment and timepoint. The trough plasma concentration of itraconazole, hydroxy-itraconazole, and carbamazepine will be listed by subject and summarized using descriptive statistics, as applicable.

Noncompartmental PK analysis will be performed to estimate the PK parameters for OPC-167832.

The PK parameters that will be estimated are: C_{max}, AUC_t, AUC_∞, time to maximum (peak) plasma concentration (t_{max}), apparent clearance of drug from plasma after extravascular administration (CL/F), body weight normalized CL/F/BW, terminal phase elimination half-life ($t_{1/2,z}$). Other PK parameters, including those for metabolites, may be reported depending on the concentration data collected. Pharmacokinetic parameters will be summarized by treatment and timepoint using the same descriptive statistics as for concentrations plus geometric mean and geometric % CV. Values of t_{max} will be summarized as median, minimum, and maximum.

11.1 Statistical Analyses of Primary Pharmacokinetic Endpoints

The effect of itraconazole or carbamazepine administration on the single-dose PK of OPC-167832 will be assessed using the primary PK parameters of OPC-167382: C_{max}, AUC_t, and AUC_∞ in the presence and absence of either itraconazole or carbamazepine.

Statistical analyses will be performed using the log-transformed PK parameters. The magnitude of the DDI will be assessed by computing the ratio of the geometric means of the OPC-167832 + potentially interacting drug versus OPC-167832 alone and the corresponding 90% confidence intervals (CIs) based on the log-transformed data.

An analysis of variance will be performed on the log-transformed PK parameters C_{max}, AUC_t, and AUC_∞ for OPC-167832 and/or its metabolites using the MIXED procedure in SAS for each part separately. The mixed-effects linear model for each PK parameter will include treatment (OPC-167832 + potentially interacting drug [test] and OPC-167832 alone [reference]) as a fixed effect and subject as a random effect. From each analysis, mean differences between the treatments OPC-167832 + potentially interacting drug and OPC-167832 alone and the 90% CI for the differences will be derived. The antilog of the differences will then provide an estimate of the geometric mean ratios (GMR; OPC-167832 + potentially interacting drug/OPC-167832 alone), and the antilog of the confidence limits will provide the 90% CIs (to at least 2 decimal places) for the GMRs.

SAS code for these analyses are outlined in Appendix 6.

11.2 Statistical Analyses of Secondary Pharmacokinetic Endpoints

Not applicable.

11.3 Technical Details of Pharmacokinetic Statistical Analyses

Not applicable.

12 Pharmacodynamic Analyses

Not applicable.

14 Interim Analysis

None.

15 Changes in Planned Analysis

None.

16 References

1 United States Department of Health and Human Services, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events; 2017 (version 2.1).

17 Document History

Dates/Author	Description of Updates	Version	Document Updates
26 September 2022/ CCI [redacted]	draft	1.0	Not Applicable
25 January 2023/ CCI [redacted]	draft: 1) updated Appendix 1. Criteria now includes only parameters relevant to the study. 2) updated Appendix 2. The entire DAIDS table has been included as Appendix 2. 3) included QTxx > 480 msec (males and females) criterion for QT, QTcF and QTcB in Appendix 5. 4) clarified collection of relatedness of adverse events to IMP and its components. 5) Other minor updates to text for greater clarity and readability.	1.1	Applied.
13 March 2023/ CCI [redacted]	Final version: 1) clarifications to text	1.0	

Appendix 1 Definition of Grades in Serum Chemistry, Hematology and Urinalysis Lab Test Results in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

The table below contains reference to the criteria provided in the DAIDS table. The DAIDS table v2.1 is attached as Appendix 2 to this SAP.

Protocol Assessment	DAIDS Grading Table Row(s)	Page in DAIDS grading tables
Hematology		
Hemoglobin	Hemoglobin, Low (≥ 13 years of age (female only)	29
	Hemoglobin, Low (≥ 13 years of age (male only)	29
Hematocrit	-	-
Mean corpuscular hemoglobin concentration	-	-
Mean corpuscular volume	-	-
RBC count	-	-
WBC count (absolute and differential)	WBC, Decreased	30
Platelets	Platelets, Decreased	30
Serum Chemistry		
Alkaline phosphatase	Alkaline phosphatase, High	25
Alanine aminotransferase	ALT or SGPT, High	25
Aspartate aminotransferase	AST or SGOT, High	25
Bilirubin, total (with reflex if elevated)	Total bilirubin, High	25
Blood urea nitrogen	-	-
Calcium	Calcium, High	26
	Calcium, Low	27
	Calcium (ionized), Low	28
Cholesterol	Cholesterol, Fasting, High	27
Creatinine	Creatinine, High	26
	Creatinine Clearance or eGFR, Low	26
Gamma glutamyl transferase	-	-
Glucose	Glucose, Fasting, High	26
	Glucose, Nonfasting, High	26
	Glucose, Low	27
Lactate dehydrogenase	Lactate, High	27
Magnesium	Magnesium, Low	27
Potassium	Potassium, Low	27

	Potassium, High	27
Protein, total	-	-
Sodium	Sodium, High	28
	Sodium, Low	28
Triglycerides	Triglycerides, Fasting	27
Urinalysis		
Glucose or glycosuria	Glycosuria	31
Blood or hematuria	Hematuria	31
Protein or proteinuria	Proteinuria	31
Drug screen	-	-
Additional Tests		
Urine or serum pregnancy test	-	-
Follicle-stimulating hormone for post-menopausals	-	-
Serology (hepatitis B surface antigen, hepatitis C antibodies, human immunodeficiency virus)	-	-

Appendix 2 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1, July 2017)

Glossary and Acronyms	
Acronym	**Definition**
AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (***serum glutamic pyruvic transaminase)***
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (***serum glutamic-oxaloacetic transaminase)***
AV	Atrioventricular
Basic Self-care Functions	Adult: Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children: Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (eg, for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.

Glossary and Acronyms

Acronym	Definition
INR	International normalized ratio
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (ie, it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children: Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAID S-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term “severe” is not the same as the term “serious” in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (ie, safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (eg, signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs

When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes

In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades

If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values

General

An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values Below Grade 1

Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges

When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory value. For example, “Magnesium, Low" has a

grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage

Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies

In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (ie, the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

Estimating Severity Grade for Parameters Not Identified in the Grading Table				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causng inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions

Cardiovascular				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalitiesa ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)*				
≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, hieght, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

Cardiovascular				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with acute significant blood loss)				
> 16 years of age	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Intervalb	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (eg, Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

a Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10. 1542/peds.2009-2107C.

b As per Bazett's formula.

Dermatologic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritusa (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

Dermatologic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

a For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.

Endocrine and Metabolic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy[a]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

Endocrine and Metabolic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lipohypertrophy[b]	Detectable by study participant, caregiver, pr physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

a Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
b Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite with significant weight loss	Life-threatening consequences OR Aggressive intervention (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation needed	Life-threatening consequences (eg, obstruction)
Diarrhea				
≥ 1 year of age	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24 hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline 24 hour period	Increase of ≥ 7 stools per 24 hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)

Gastrointestinal				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (eg, hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indication	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA

Gastrointestinal				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

Musculoskeletal				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findigns OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[a]				
> 30 years of age	BMD t-score −2.5 to −1	NA	NA	NA
< 30 years of age	BMD z-score −2 to −1	NA	NA	NA
Osteoporosis[a]				
> 30 years of age	NA	BMD t-score < −2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMZ z-score < −2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

a BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (eg, stroke with neurological deficit)
Altered Mental State (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbances (includes dementia and attentional deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay < *18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

Neurologic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurological function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to eprform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal parasthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (eg, epilepticus) OR Difficult to control (eg, refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR 24 hours postictal state	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)

Neurologic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Syncope	Near syncope without loss of consciousness (eg, pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[a] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

a Definition: A pregnancy loss occurring at < 20 weeks gestational age

Psychiatric				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

Sensory				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not required	Hearing aid or intervention required	Profound bilateral hearign loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (ie, > 50 dB audiogram and < 50% speech discrimination)
< 12 years of age based on a 1, 2, 3, 4, 6, and 8 kHz audiogram	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Sensory				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interferences with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[a]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	> 38.6 to < 39.3°C or > 101.5 to < 102.7°F	> 39.3 to < 40.0°C or > 102.7 to < 104.0°F	> 40.0°C or > 104.0°F
Pain[b] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

Systemic				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Serum Sickness[c]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)
Underweight[d] *> 5 to 19 years of age*	WHO BMI z-score < −1 to −2	WHO BMI z-score < −2 to −3	WHO BMI z-score < −3	WHO BMI z-score < −3 with life-threatening consequences
2 to 5 years of age	WHO weight-for-height z-score < −1 to −2	WHO weight-for-height z-score < −2 to −3	WHO weight-for-height z-score < −3	WHO weight-for-height z-score < −3 with life-threatening consequences
< 2 years of age	WHO weight-for-length z-score < −1 to −2	WHO weight-for-length z-score < −2 to −3	WHO weight-for-length z-score < −3	WHO weight-for-length z-score < −3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

a Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

b For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.

c Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

d WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http ://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Rednessa *Report only one*				
> 15 years of age	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR > 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
< 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥ 50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one*	Same as for **Injection Site Erythema or Redness,**	Same as for **Injection Site Erythema or Redness,**	Same as for **Injection Site Erythema or Redness,**	Same as for **Injection Site Erythema or Redness,**
> 15 years of age	*> 15 years of age*	*> 15 years of age*	*> 15 years of age*	*> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *< 15 years of age*	Same as for **Injection Site Erythema or Redness,** *< 15 years of age*	Same as for **Injection Site Erythema or Redness,** *< 15 years of age*	Same as for **Injection Site Erythema or Redness,** *< 15 years of age*

Site Reactions to Injections and Infusions				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

a Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values

An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

Chemistries				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life- threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 2.0*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin*a*, High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (eg, signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	> 5.0 × ULN
≤ 28 days of age	See Table: Total Bilirubin for Term and Preterm Neonates	See Table: Total Bilirubin for Term and Preterm Neonates	See Table: Total Bilirubin for Term and Preterm Neonates	See Table: Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L)* *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*

Chemistries				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Calcium (Ionized), High (mg/dL; *mmol/L)*	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L)* *≥ 7 days of age* *< 7 days of age*	 7.8 to < 8.4 *1.95 to < 2.10* 6.5 to < 7.5 *1.63 to < 1.88*	 7.0 to < 7.8 *1.75 to < 1.95* 6.0 to < 6.5 *1.50 to < 1.63*	 6.1 to < 7.0 *1.53 to < 1.75* 5.50 to < 6.0 *1.38 to < 1.50*	 < 6.1 *< 1.53* < 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L)*	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 × ULN	6 to < 10 × ULN	10 to < 20 × ULN	≥ 20 × ULN
Creatinine, High *Report only one*	1.1 to 1.3 × ULN	> 1.3 to 1.8 × ULN OR Increase to 1.3 to < 1.5 × participant's baseline	> 1.8 to < 3.5 × ULN OR Increase to 1.5 to < 2.0 × participant's baseline	≥ 3.5 × ULN OR Increase of ≥ 2.0 × participant's baseline
Creatinine Clearanceb or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L)* ***Fasting, High*** ***Nonfasting, High***	 110 to 125 *6.11 to < 6.95* 116 to 160 *6.44 to < 8.89*	 > 125 to 250 *6.95 to < 13.89* > 160 to 250 *8.89 to < 13.89*	 > 250 to 500 *13.89 to < 27.75* > 250 to 500 *13.89 to < 27.75*	 ≥ 500 *≥ 27.75* ≥ 500 *≥ 27.75*
Glucose (mg/dL; *mmol/L)* ***Fasting, Low*** *≥ 1 month of age* *< 1 month of age*	 55 to 64 *3.05 to < 3.55* 50 to 54 *2.78 to < 3.00*	 40 to < 55 *2.22 to < 3.05* 40 to < 50 *2.22 to < 2.78*	 30 to < 40 *1.67 to < 2.22* 30 to < 40 *1.67 to < 2.22*	 < 30 *< 1.67* < 30 *< 1.67*
Lactate, High	ULN to < 2.0 × ULN without acidosis	≥ 2.0 × ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

Chemistries				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lipase, High	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	> 300 to 500 *> 3.42 to 5.7*	> 500 to < 1,000 *> 5.7 to 11.4*	> 1,000 *> 11.4*
Magnesiumc, Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to 160*	> 160 *> 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	< 120 *< 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	> 15.0 *> 0.89*

a Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

b Use the applicable formula (ie, Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

c To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Hematology				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 100 to < 200	< 100 < 100
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 × 10^9 to < 0.650 × 10^9*	500 to < 600 *0.500 × 10^9 to < 0.600 × 10^9*	350 to < 500 *0.350 × 10^9 to < 0.500 × 10^9*	< 350 *< 0.350 × 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 × 10^9 to 1.000 × 10^9*	600 to 799 *0.600 × 10^9 to 0.799 × 10^9*	400 to 599 *0.400 × 10^9 to 0.599 × 10^9*	< 400 *< 0.400 × 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 × 10^9 to 1.500 × 10^9*	1,000 to 1,249 *1.000 × 10^9 to 1.249 × 10^9*	750 to 999 *0.750 × 10^9 to 0.999 × 10^9*	< 750 *< 0.750 × 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 × 10^9 to 5.000 × 10^9*	3,000 to 3,999 *3.000 × 10^9 to 3.999 × 10^9*	1,500 to 2,999 *1.500 × 10^9 to 2.999 × 10^9*	< 1,500 *< 1.500 × 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 × LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 × LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 × LLN	< 50 *< 0.50* OR < 0.25 × LLN OR Associated with gross bleeding
Hemoglobina, Low (g/dL; *mmol/L*)b				
> 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*

Hematology				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
8 to < 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
< 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 × ULN	1.5 to < 2.0 × ULN	2.0 to < 3.0 × ULN	> 3.0 × ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	> 20.0%
PTT, High (not on anticoagulation therapy**)**	1.1 to < 1.66 × ULN	1.66 to < 2.33 × ULN	2.33 to < 3.00 × ULN	> 3.00 × ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100,000 × 10^9 to 125,000 × 10^9*	50,000 to < 100,000 *50,000 × 10^9 to < 100,000 × 10^9*	25,000 to < 50,000 *25,000 × 10^9 to < 50,000 × 10^9*	< 25,000 *< 25,000 × 10^9*
PT, High (not on anticoagulation therapy)	1.1 to < 1.25 × ULN	1.25 to < 1.50 × ULN	1.50 to < 3.00 × ULN	> 3.00 × ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2,000 × 10^9 to 2,499 × 10^9*	1,500 to 1,999 *1,500 × 10^9 to 1,999 × 10^9*	1,000 to 1,499 *1,000 × 10^9 to 1,499 × 10^9*	< 1,000 *< 1,000 × 10^9*
< 7 days of age	5,500 to 6,999 *5,500 × 10^9 to 6,999 × 10^9*	4,000 to 5,499 *4,000 × 10^9 to 5,499 × 10^9*	2,500 to 3,999 *2,500 × 10^9 to 3,999 × 10^9*	< 2,500 *< 2,500 × 10^9*

a Male and female sex are defined as sex at birth. For transgender participants ≥ 13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (ie, a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

b The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Urinalysis				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Total Bilirubin Table for Term and Preterm Neonates				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Total Bilirubina, High (mg/dL; *µmol/L*)b				
Term Neonate				
< 24 hours of age	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7to 28 days of age (breastfeeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
Preterm Neonatec				
35 to < 37 weeks gestational age	Same as for **Total Bilirubin, High, Term Neonate** (based on days of age).	Same as for **Total Bilirubin, High, Term Neonate** (based on days of age).	Same as for **Total Bilirubin, High, Term Neonate** (based on days of age).	Same as for **Total Bilirubin, High, Term Neonate** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breastfeeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breastfeeding)	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN

a Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

b A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

c Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age, and neonate, as 0 to 28 days of age.

Appendix 3 Criteria for Potentially Clinically Significant Vital Sign Abnormalities

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate	> 110 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure	> 160 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Weight	Not Applicable	≥ 5% increase ≥ 5% decrease
Respiratory Rate	< 12 breaths/min or > 20 breaths/min	Not Applicable
Temperature	< 36°C or > 38°C	Not Applicable

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 4 Definition of Grades for Vital Sign in the Division of AIDS Table[1] for Grading the Severity of Adult and Pediatric Adverse Events

The table below contains some of the criteria provided in the DAIDS table. Please see pages of the DAIDS v2.1 tables available in Appendix 2 for details for blood pressure abnormalities, unintentional weight loss, fever.

Abnormality	AGE GROUP	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Hypertension (with the lowest reading taken after repeat testing during a visit) Male/Female	≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR hospitalization indicated
Unintentional Weight Loss (excludes postpartum weight loss)		NA	5% to < 9% loss in body weight from baseline	≥ 9% to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Fever (non-axillary temperatures only)		38.0°C to < 38.6°C or 100.4°F to < 101.5°F	≥ 38.6°C to < 39.3°C or ≥ 101.5°F to < 102.7°F	≥ 39.3°C to < 40.0°C or ≥ 102.7°F to < 104.0°F	≥ 40.0°C or ≥ 104.0°F

Appendix 5 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Category Diagnosis	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	110 bpm	increase of 15 bpm
Bradycardia	50 bpm	decrease of 15 bpm
Rhythm		
Sinus tachycardia[b]	110 bpm	increase of 15 bpm
Sinus bradycardia[c]	50 bpm	decrease of 15 bpm
Supraventricular premature beat	All	not present → present
Ventricular premature beat	All	not present → present
Supraventricular tachycardia	All	not present → present
Ventricular tachycardia	All	not present → present
Atrial fibrillation	All	not present → present
Atrial flutter	All	not present → present
Conduction		
1° atrioventricular block	PR > 0.20 s	not present → present
2° atrioventricular block	All	not present → present
3° atrioventricular block	All	not present → present
Left bundle-branch block	All	not present → present
Right bundle-branch block	All	not present → present
Pre-excitation syndrome	All	not present → present
Other intraventricular conduction block[d]	QRS > 0.12 s	increase of 0.02 s
Infarction		
Acute or subacute	All	not present → present
Old	All	not present → present 12 weeks post trial entry
ST/T Morphological		
Myocardial Ischemia	All	not present → present
Symmetrical T-wave inversion	All	not present → present
Increase in QT	QT > 450 msec (males and females)	-
	QT > 480 msec (males and females)	-
	QT > 500 msec (males and females)	-
Increase in QTcF	QTcF > 450 msec (males and females)	-
	QTcF > 480 msec (males and females)	-
	QTcF > 500 msec (males and females)	-
		Increase of ≥ 30 msec and ≤ 60 msec
		Increase of > 60 msec
Increase in QTcB	QTcB > 450 msec (males and females)	-

Category **Diagnosis**	**Criterion Value[a]**	**Change Relative to Baseline[a]**
	QTcB > 480 msec (males and females)	-
	QTcB > 500 msec (males and females)	-
		Increase of ≥ 30 msec and ≤ 60 msec
		Increase of > 60 msec

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" OR represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b]No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c]No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d]No current diagnosis of left bundle branch block or right bundle branch block.

Appendix 6 Technical Details

The following code illustrates the program statements that could be used to fit the linear mixed effect model using the MIXED procedure in SAS. The independent variable will be treatment (A=OPC-167832 alone, and B=OPC-167832 and itraconazole). Analyses will be performed using the log-transformed PK parameters.

Y denotes the response variable (eg, the log-transformed C_{max}, AUC_t or AUC_∞). The alpha level is set to 0.1 so that a two-sided 90% CI will be produced as model estimation. The standard error for difference is calculated using Satterthwaite approximation for two groups with unequal variance.

```
PROC MIXED CL ALPHA=0.1;
        CLASS SUBJECT TREATMENT ;
        MODEL Y = TREATMENT / DDFM=SATTERTH;
        RANDOM SUBJECT ;
        LSMEANS TREATMENT / CL ALPHA=0.1;
        ESTIMATE 'B VS A' TREATMENT -1 1  / CL ALPHA = 0.1; * Part 1;
RUN;
```

The ESTIMATE statement will be used to obtain the least square estimate of the difference between treatments, the standard error associated with the difference, and the corresponding 90% CI.

The antilog of the differences will then provide an estimate of the geometric mean ratios (GMR;OPC-167832 + potentially interacting drug/OPC-167832 alone), and the antilog of the confidence limits will provide the 90% CIs for the GMRs.

Part 2

The following code illustrates the program statements that could be used to fit the linear mixed effect model using the MIXED procedure in SAS for Part 2 data.

Y denotes the response variable (eg, the log-transformed C_{max}, AUC_t or AUC_∞). (D=OPC-167832 alone, and E=OPC-167832 and carbamazepine). The alpha level is set to 0.1 so that a two-sided 90% CI will be produced as model estimation. The standard error for difference is calculated using Satterthwaite approximation for two groups with unequal variance.

```
PROC MIXED CL ALPHA=0.1;
```

```
CLASS SUBJECT TREATMENT ;
MODEL Y = TREATMENT / DDFM=SATTERTH;
RANDOM SUBJECT ;
LSMEANS TREATMENT / CL ALPHA=0.1;
ESTIMATE 'E VS D' TREATMENT -1 1 0 / CL ALPHA = 0.1;
RUN;
```

The ESTIMATE statement will be used to obtain the least square estimate of the difference between treatments, the standard error associated with the difference, and the corresponding 90% CI. The antilog of the differences will then provide an estimate of the geometric mean ratios (GMR;OPC-167832 + potentially interacting drug/OPC-167832 alone), and the antilog of the confidence limits will provide the 90% CIs for the GMRs.

Otsuka

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