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Subject: Safety and effectiveness of DTG use in pregnancy.**Author(s):**

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MARKETING AUTHORISATION HOLDER(S)

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ADRs	Adverse Drug Reactions
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
AR	Adverse Reaction
ARV	Antiretroviral
APR	Antiretroviral Pregnancy Registry
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CROI	Conference on Retroviruses and Opportunistic Infections
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EC	Ethics Committee
EMA	European Medicines Agency
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
EU	European Union
EUCTD	European Clinical Trials Directive
EudraVIGILANCE	European Database for Pharmacovigilance
EUROCAT	European Surveillance of Congenital Anomalies
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Hazard Ratio
HIV	Human Immunodeficiency Virus
IAS	International AIDS Society
ICF	Informed Consent
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IECs	Independent Ethics Committees
IMP	Investigational Medicinal Product
INSTI	Integrase Strand Transfer Inhibitor
IRBs	Institutional Review Boards
3TC	Lamivudine
MA	Marketing Authorisation
MS	Member State
NEAT ID	The European AIDS Treatment Network
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
OR	Odds Ratio

PASS	Post-authorization Safety Study
PI	Principal Investigator
PENTA	Paediatric European Network for Treatment of AIDS
QA	Quality Assurance
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RPV	Rilpivirine
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Statistical Analysis Software
SmPC	Summary of Product Characteristics
SPSS	Statistical Package for the Social Sciences
sPVP	Study-specific Pharmacovigilance Plan
VL	Viral Load

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TRIUMEQ
JULUCA

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

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CONFIDENTIAL

eTrack Project Number: 208759

Protocol Amendment: DOLOMITE NEAT ID Network Study: A prospective, multi-site observational study to define the safety and effectiveness of Dolutegravir use in HIV positive pregnant women

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3. ABSTRACT

In 2014, the European Commission recommended the authorisation of Dolutegravir (DTG) an integrase strand transfer inhibitor, marketed as a single agent as Tivicay®, and also Triumeq®, a fixed dose combination (FDC) tablet containing DTG/abacavir (ABV)/lamivudine (3TC), for use in the European Union for the treatment of adults and adolescents aged 12 years and older with HIV-1 in combination with other antiretroviral agents. In clinical trials including adult patients, the most commonly reported adverse drug reactions (ADRs) to Tivicay were nausea, diarrhoea and headache. A more serious but less common side effect is hypersensitivity reaction with rash and possible effects on the liver.

DTG-containing regimens are recommended during pregnancy only if the potential benefit outweighs the potential risk to the foetus as per the summary of product characteristics (SmPC). In May 2018, preliminary findings from an unscheduled analysis of a birth outcomes surveillance study conducted in Botswana showed a higher than expected number of neural tube defects (NTDs) among newborns whose mothers were exposed to dolutegravir (DTG)-based anti-retroviral therapy (ART) at time of conception. The findings were part of the Tsepamo study, an NIH/NICHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. Following the release of the Tsepamo study data, EMA and FDA guidance recommend that due to the potential risk of NTD and the absence of a known mechanism women should not become pregnant whilst on dolutegravir and dolutegravir use should be avoided during the first trimester^{1,2}

In 2016 there were 34,179 new HIV infections among women 20-39 years old³. With the average European growth rate of 0.1 in 2015-2060 approximately 3,400 deliveries annually could be expected only in this population of HIV positive women⁴. The new EMA, FDA guidance may lead to fewer pregnancies occurring on dolutegravir from now on.

This multi-site observational study is expected to enrol between 250 and potentially up to 500 HIV positive pregnant women receiving DTG, at least 200 starting, or on DTG in first trimester and the rest starting in any trimester. The data collected will be that obtained during routine standard of care assessments; and the participant will not undergo any interventional study procedures. The study will aim to define the safety profile and effectiveness of DTG in this patient population by:

- Reporting pregnancy and birth outcomes.
- Describing incidence rate of discontinuation of DTG in pregnancy, including reasons and HIV viral load at discontinuation.
- Providing descriptive safety data in relation to DTG (incidence and severity of all drug related adverse events (AEs) and serious adverse events (SAEs)).

4. AMENDMENTS AND UPDATES

Amendment or Update No	Date	Section of Study Protocol	Amendment or Update	Reason
1	13/Nov/2018	Abstract/Background	Updated background information to include language on NTD issue	Newly presented data since original protocol was signed off
1	13/Nov/2018	Study Design	Updated study design to include ALL pregnancies exposed to DTG based regimen from participating sites since the approval and availability of DTG	There is anticipated lower use of DTG during pregnancy and hence changed the study design to include retrospective cases also
1	13/Nov/2018	Study Design/Study Population and Setting/Data Source	Added the inclusion of Canadian sites	The lead investigator of the Canadian perinatal surveillance study has agreed to participate in the study

5. MILESTONES

Milestone	Planned date
Start of data collection	March/April-2019
End of data collection	tbd
Annual progress reports	Yearly, within 30 days of the anniversary date of EC approvals.
Final report of study results	tbd

6. RATIONAL AND BACKGROUND

Dolutegravir is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Tivicay® and Triumeq® are indicated for use in HIV-infected patients who are treatment naïve or previously treated. In adults, the use of DTG includes for those with suspected or documented resistance to integrase inhibitors. In clinical trials including adult patients, the most commonly reported adverse drug reactions (ADRs) to Tivicay were nausea, diarrhoea and headache. A more serious but less common side effect is hypersensitivity reaction with rash and possible effects on the liver.

In animal and ex vivo human placenta perfusion studies, DTG has been shown to have a high penetration across the placenta, unlike some other antiretrovirals, where this might protect a developing embryo against vertical HIV transmission, but might also increase the risk of adverse birth outcomes^{5,6}. In animal toxicology studies¹¹, there has been no evidence for adverse effects from DTG treatment during pregnancy⁷. In May 2018, preliminary findings from an unscheduled analysis of a birth outcomes surveillance study conducted in Botswana showed a higher than expected number of neural tube defects (NTDs) among newborns whose mothers were exposed to dolutegravir (DTG)-based anti-retroviral therapy (ART) at time of conception (4 NTD cases out of 426 pregnancies on dolutegravir). This represents an incidence of about 0.9% with an expected background rate of about 0.1%.

The Tsepamo study is an NIH/NICHD-funded birth outcomes surveillance study evaluating adverse birth outcomes by HIV-status and ART regimen and risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception, with an anticipated surveillance of ~95,000 births over four years (August 2014-August 2018). The Tsepamo study is still ongoing, and it is anticipated that birth outcomes from at least another 600 women who have already become pregnant while receiving dolutegravir from prior to conception will be captured in the ongoing surveillance over the next 9 months (May 2018 to February 2019). In view of this, DTG- containing regimens are recommended during pregnancy only if the potential benefit outweighs the potential risk to the foetus as per the summary of product characteristics (SmPC).

This multi-site observational study will include all pregnancies exposed to DTG based regimen since its approval and availability in 2014 to further assess the safety and effectiveness of DTG use in pregnancy in “real world” settings in Europe and Canada.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The aim for this study is to assess the safety and effectiveness of DTG use in HIV positive pregnant women in a “real world” setting.

7.1. Study Objective(s)

7.1.1. Primary Objective

1. To describe pregnancy and birth outcomes; Pregnancy outcomes include spontaneous abortion, induced abortion, still births, multiple births, type of delivery and maternal viral load (VL) at delivery. Birth outcomes include birth defects (to be reported in real-time to the Antiretroviral Pregnancy Registry: <http://www.apregistry.com/>) and other routinely collected data at birth such as gestational age, birth weight, APGAR score and infant’s HIV status.

7.1.2. Secondary Objectives

1. To provide descriptive analysis of all drug related AEs and SAEs related with the regimen used. These will be categorised by trimester of initiation.
2. To describe rate of DTG discontinuation in pregnant women, including reasons and VL at discontinuation and viral suppression during each of the trimesters where possible.

8. RESEARCH METHODS

8.1. Study Design

This is a 3 year multi-site observational study, enrolling between 250 and potentially up to 500 HIV positive pregnant women exposed to DTG. The enrolment period will be over 2 years with follow-up period of 1 year for outcomes from approximately 35-50 clinical sites from Europe and Canada.

Potential investigational sites from across Europe and Canada will be contacted for feasibility and selection will be based on sites having used DTG as a treatment option for pregnant women or are using DTG in pregnancy. There will be no additional data collected in this observational study outside of the current routine standard of care at each investigational site.

8.2. Study Population and Setting

8.2.1. Inclusion Criteria

The study population will be comprised of:

1. HIV positive pregnant women aged 18 years and over who were/are exposed to DTG at least once during their pregnancy,
2. With or without maternal or birth outcomes,
3. Able and willing to provide written informed consent (as locally required) and comply with any safety reporting requirements.

8.2.2. Patient Identification and Consent

We aim to enrol between 250 and potentially up to 500 pregnant women from approximately 35 - 50 clinical sites from Europe and Canada; at least 200 of them with first trimester exposure to DTG, and the rest starting DTG during any trimester. Once all relevant approvals are in place, selected sites will be contacted and asked to identify all women exposed to DTG during pregnancy. We are looking for sites to provide retrospective and prospective data of all pregnant women who have been exposed to DTG during their pregnancy, whether they have had a maternal or birth outcome yet or not. Consent procedures will be undertaken as required as per protocol and by country specific regulations and local procedures. The participants will not have to attend any additional visits or undergo any additional procedures above their routine standard of care.

8.3. Variables

8.3.1. Exposure Definitions

Duration of exposure to DTG will be expressed in days e.g. 40 days.

- **Exposure on this study:** This is defined as the first day DTG is known to have been taken during pregnancy. A subject may have multiple exposures defined in cases where there is re-initiation of therapy after a period of stoppage during pregnancy; reason for stoppage will be collected.
- **Person time exposed:** This is defined as the number of days that the subject is known to have been exposed to DTG. This will further be categorized by days per trimester.
- Exposure will also be categorised by trimester of exposure for the first-time during pregnancy -first trimester, second trimester and third trimester. First trimester exposures will further be stratified into a) conceived while on DTG and b) started DTG after conception.

NOTE: Initiation of pregnancy is measured as gestational age which is taken from the woman's last menstrual period, or the corresponding age of the gestation as estimated by a more accurate method such as ultrasound, if available.

8.3.2. Outcome Definitions

8.3.2.1. Primary Outcomes

- a) The primary effectiveness parameters will be maternal VL at delivery and neonatal HIV status.
- b) The primary safety parameters will be; spontaneous abortion, induced abortion, still births/live births/, premature births, low birth weight and prevalence of birth defects.

Pregnancy Outcome/ Birth Outcome	Definition
Induced abortion	Voluntary termination of pregnancy before 22 weeks gestation
Spontaneous abortion	Death of a fetus or expulsion of the products of conception before 22 weeks gestation
Low birth weight	Birth weight of <2500 grams
Very low birth weight	Birth weight of <1500 grams
Extremely low birth weight	Birth weight of <1000 gms
Preterm birth	Birth of live infant at <37 weeks gestation
Severely preterm birth	Birth of live infant at <32 weeks gestation
Stillbirth	Death of a fetus occurring at 22 weeks of gestation or more, or for situations in which the gestational age is unavailable, a fetus weighing at least 500 grams
Birth defects	To be classified according to the World Health Organization's International Classification of Diseases, Tenth Revision

Table 1. Definitions of pregnancy outcomes.

8.3.2.2. Secondary Outcomes

- a) All drug related AEs
- b) All drug related SAEs
- c) Virological failure and development of integrase resistance,
- d) Incidence of discontinuation of DTG in pregnancy, reasons and VL at discontinuation
- e) Where available, VL during each of the three trimesters to assess suppression

8.3.3. Confounders

The effect of the following potential confounders on the risk for outcomes of interest will be examined:

- Prior or current AIDS defining illness and/or nadir CD4 count (<50, <200, >200 cells/mm³), if available,
- Concomitant medications (including ARVs and other medications that have been described to be associated with hypersensitivity reaction [HSR], skin reactions, or liver chemistry elevations [LCT] elevations),

- Co-morbidities,
- Race /ethnicity,
- Duration of DTG exposure during pregnancy,
- Trimester of DTG initiation,
- Treatment experience level, switch or naïve,
- Persistent VL during pregnancy,
- Number of prior pregnancies(gravida),
- History of prior abortions, premature births and low weight births,
- History of smoking, alcohol and drug use during pregnancy,
- History of TORCH (Toxoplasmosis, Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus [CMV], and Herpes) infections during pregnancy,
- History of birth defects in previous births

8.4. Data Source

Data will be collected from all participating European and Canadian sites. Following all relevant approvals, selected sites will be contacted and asked to identify all women on DTG during pregnancy and collect data retrospectively and prospectively for these patients, whether they have had a maternal or birth outcome yet or not. Data relevant to the study objectives will be abstracted from the patients' medical records. The participants will not have to attend any additional visits or undergo any procedure above their routine standard of care. Anonymised data will be collected either by electronic transfer of datasets from each site or entered into a secure eCRF platform dependent on their capabilities (there will be no transferal of personal identifiers to the NEAT ID Data Centre).

Upon enrolment, the eCRF will produce a unique code for each subject for data reference purposes (the unique code will enable the depersonalization of data; where the participant's identifying information is replaced by an unrelated sequence of characters, only sites will have access to the de-coded lists. The NEAT ID Data Centre will not have access to de-coded lists. Sites will be monitored for data quality and accuracy as per the risk-based monitoring plan for the study.

The following data will be collected if available for each participant and updated information included in the 3 monthly data transfer. The data table is summarised in the flow chart in Appendix 1.

1. Baseline characteristics such as age, ethnicity, medical and social history, nadir CD4, prior or current AIDs defining illness at time of starting pregnancy.
2. Date of start of pregnancy.
3. Date of starting DTG.
4. Latest data on CD4 count, VL, ARV drug history with dates, within 12 months prior to starting pregnancy, where available.
5. ARV drug history with dates of starting and reasons for stopping during pregnancy.
6. Co-morbidities and all co-medications.
7. Where available, HIV RNA and CD4 count data at time of enrolment and once every 3 months until delivery and also at time of starting DTG.
8. VL at DTG discontinuation during pregnancy, if applicable.
9. Resistance tests results of any HIV resistance tests performed during pregnancy.
10. All drug related AEs and SAEs: timing in pregnancy, incidence and severity.
11. Pregnancy outcomes including spontaneous abortion, induced abortion, still births, multiple births, live births, type of delivery (normal delivery, forceps delivery, or cesarean) and VL at delivery.
12. Birth outcomes including birth defects with date (to be reported in real-time to the Antiretroviral Pregnancy Registry) and other routinely collected data at birth such as gestational age, birth weight, APGAR score.

13. Postpartum CD4 count and VL.
14. HIV status of the newborn infant.

A pooled analysis (individual patient data) on birth outcomes (spontaneous and induced abortions, birth defects, preterm delivery, small-for-gestational age, stillbirth) among mother-infant pairs with first trimester exposure using data collected within DOLOMITE-NEAT ID and DOLOMITE-EPPICC will be conducted at the end of the study period, with appropriate de-duplication for any mother-infant pairs that are in both datasets.

8.5. Study Size

This is a non-interventional, observational study where no formal samples size calculation is to be performed. The Antiretroviral Pregnancy Registry (APR) has estimated that based on the prevalence of birth defects in the general population, 200 first trimester exposures are needed to detect two-fold increase in overall birth defect rate⁷. While this is specific to APR, EUROCAT⁸ has reported similar or slightly higher birth defect rates.

8.6. Data Management

8.6.1. Data Collection

8.6.1.1. Source Data

Source data are contained in source documents (original records or certified copies) maintained at site. No additional data will be collected for this study, data will be collected from routine standard of care data only.

8.6.1.2. Source Documents

Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study) will be maintained at site in accordance with usual standard of care.

The subject's number and date of entry into the study, along with a study identifier, should be recorded in the subject's study records.

8.6.1.3. Data Collection Methods

In order to maintain confidentiality, the subject will be identified only by unique subject number.

Anonymised subject data will be collected either via extraction from electronic source data by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the Principal Investigator (PI) or by direct entry into a secure eCRF platform. A delegation of responsibility log will be updated accordingly. Sites will provide (in to the eCRF) / or upload data in to a secure data repository portal, every three months. The NEAT ID Data Centre will store the data on a secure network with access to authorised personnel of the data management team only and maintain a log of authorised personnel.

8.6.2. Data Handling Conventions

Data will be handled in accordance with data handling guidelines provided to sites.

The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required. Identified only by unique subject number, the deidentified data are transferred

securely and all transfers are fully documented.

8.6.3. Resourcing Needs

The study will be overseen and managed by NEAT ID. NEAT ID will assign a Project Manager to the study who will oversee the day to day activities and manage the multidisciplinary project team.

ViiV, as sponsor will retain all responsibilities in relation to regulatory reporting.

8.6.4. Timings of Assessment During Follow-up

Available data will be collected from enrolled participants every 3 months and transferred to the data coordinating centre. Participant involvement in this study will end after the birth and pregnancy outcome data is collected.

8.7. Data Analysis

A detailed statistical analysis plan will be produced during the early stages of the study, after protocol finalization. This statistical analysis plan will describe the rules used for classification of safety data, the primary and secondary analysis and the format of the final tables, figures and listings to be generated.

8.7.1. Essential Analysis

Descriptive report will be generated for the following:

- Maternal Characteristics,
- ARV history and concomitant medication,
- Co-morbidities,
- Trimester of DTG initiation and exposure,
- Drug related AEs and SAEs,
- Incidence of DTG discontinuation,
- VL in each trimester, at delivery and at DTG discontinuation,
- Maternal and child outcomes.

Analysis will be conducted to assess if there are any associations between DTG exposure and outcomes for pregnancy and birth. Logistic regression and Cox proportional-hazards models will be used. Potential confounding factors will be included in a step-wise approach to determine whether they change the odds ratio (OR) or the hazard ratio (HR) for DTG exposure by at least 10% in any of the models. Factors modifying the risk for DTG exposure by at least 10% in any of the models will be retained. Final models will be adjusted on the selected confounders.

8.8. Quality Control and Quality Assurance

Electronic data sets will provide an unmonitored subset of existing source data that will be subject to data validation. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process. Data will be analysed by a Statistician skilled in population-based analysis using SAS, SPSS or STATA.

NEAT ID may decide to include this study in the annual audit schedule. The audit conduct and reporting will be performed by the independent QA personnel and in accordance with Good Clinical Practice (GCP) and the applicable Standard Operating Procedures.

8.9. Limitations of the Research Methods

Limitations of this study are common to non-randomized observational studies. Selection bias may be present as the sites may elect to enrol participants that may have a better or worse health status compared to the general HIV positive pregnant population. Channeling bias in prescribing DTG may also be present.

8.9.1. Study Closure/ Uninterpretability of Results

Both the sponsor and the NEAT ID collaboration reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies, Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). In terminating the study, sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

Following completion of the study, any study documentation will be retained by the Investigator in accordance with GCP and applicable regulatory requirements.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval

Before the start of data collection, this protocol and any accompanying material to be provided to the patients (such as advertisements, subject information sheets as locally applicable, or descriptions of the study used to obtain informed consent) will be submitted to Ethics Committee (EC) in the relevant countries. The investigator will not begin any study activities until approval from the EC has been documented and provided as a letter to the investigator.

Any subsequent amendments that require review by EC will not be implemented until the EC grants a Favourable Opinion for the study which will be disseminated to the investigators and sites (**NOTE:** that amendments may also need to be reviewed and accepted by the regulatory agencies and/or local EC departments before they can be implemented in practice at sites).

An annual progress report will be submitted to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. NEAT ID will produce the annual reports as required.

NEAT ID will notify the EC of the end of the study. If the study is ended prematurely, the NEAT ID will notify the EC, including the reasons for the premature termination.

9.2. Subject Confidentiality

Sites will routinely hold identifiable information on their subjects. All investigators and study site staff will comply with the requirements of the current Data Protection Regulations in Europe or Canada with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulations' core principles.

Personal information is to be collected, kept secure, and maintained in line with the following requirements:

- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.

- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If during the study, a drug related adverse event (serious or non-serious) is identified as being related to any ViiV Healthcare product, this will be reported to the GSK central safety department by email or fax. All drug related SAEs will be reported within 24 hours of first becoming aware of the event to the manufacturer, drug related non-serious AEs or incidents will be reported within 5 days of first becoming aware of the event.

Email for clinical safety mailbox: PPD

Fax (preferred): PPD

Since this is a study of DTG use in pregnancy and outcomes of pregnancy, there is no need to report incident exposures pregnancy as an AE to GSK, but adverse pregnancy outcomes deemed related to a ViiV product will be reported.

All drug related serious and non-serious AEs, or incidents associated with any ViiV Healthcare product will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP) and SAE reporting guidelines. This sPVP will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier/Vendor staff pharmacovigilance training (RAD-CDV-1281 - online training annually, on the collection and reporting of AEs through external version of myLearning).
- Investigator and site staff pharmacovigilance training (RAD-CDV-1281 - online training annually, on the collection and reporting of AEs through external version of myLearning).
- Safety-specific roles
- ADRs, SAEs, pregnancy outcomes, and incident collection and reporting processes
- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

10.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before baseline are considered to be pre-existing conditions and should be documented as medical history.

Adverse Reaction (AR) An untoward and unintended response in a participant to the study medicinal product which is related to any dose administered to that participant.

The phrase “response to the study medicinal product” means that a causal relationship between the drug and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the drug qualify as adverse reactions.

Serious Adverse Event (SAE) A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation unless hospitalization is for:
 - Routine treatment or monitoring of the studies indication, not associated with any deterioration in condition.
 - Elective or pre-planned treatment for pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study drug.
 - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of SAE given above and not resulting in hospital admission.
 - Social reasons and respite care in the absence of any deterioration in the patient’s general condition.
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect
- Is medically significant, i.e. defines as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT 3xULN and bilirubin 2xULN (>35%direct*)

*Note: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin $\geq 2xULN$, then the event is still reported as an SAE. INR elevations of >1.5 suggest severe liver injury.

	NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the study drug, based on the information provided.

“Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

10.2. Assessment of Adverse Events and Serious Adverse Events (SAE)

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and for final review and confirmation of accuracy of event information and assessments.

10.3. Assessment of Causality for Study Drugs

The relationship to study drug of each adverse event will be assessed taking into consideration the following:

- A “reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator/sub-investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The approved Product Information (SmPC) for marketed products should be used in consideration of this assessment

A causality assessment should be provided on all AE/SAE forms reported to ViiV/GSK.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The target audience includes healthcare providers, patient groups, regulatory and health authorities.

Interim and final study results will be presented annually at conferences such as but not limited to Conference on Retroviruses and Opportunistic Infections (CROI) and/or International AIDS Society (IAS), and followed by a publication in relevant peer-reviewed medical scientific journal and relevant newsletters.

11.2. Study Reporting and Publications

Within one year after the end of the study, NEAT ID will submit a final report with the results, including any publications/abstracts to the EC.

12. REFERENCES

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1. APPENDICES**13.1. APPENDIX 1: DATA ASSESSMENT TABLE**

Data Collected	Timepoints			
	Pre-pregnancy	Pregnancy	Partum	Post-partum
Informed Consent	Prior to collection of any data as per local requirements			
Age	X			
Ethnicity	X			
Country of birth (if available)	X			
Mode of HIV infection	X			
HIV medical history including: -Antiretroviral treatment history ¹ -Nadir CD4 -HIV resistance test dates and results	X	X (ARV and resistance tests)		
Gynecological history (previous pregnancies and outcomes, methods of delivery, Cervical cancer surgical treatment)	X			
Health risk factors (i.e. Smoking, alcohol, psychoactive substance use (if intravenously or not))	X	X		
HIV diagnosis date/confirmatory test date	X			
Any prior or current AIDS defining illness	X			
AIDS diagnosis date	X			
CD4 count	X	X ³		X ⁶
HIV RNA test ⁴	X	X	X	X ⁶
Pregnancy diagnosis method & date		X		
Estimated date of delivery		X		
Concomitant medication (exc cART)	X	X		
Co-morbidities ²	X	X		
TORCH infections		X		
Side effects/ toxicity		X		
*Pregnancy outcome - Date - Type of delivery: normal, forceps or cesarean - Spontaneous or induced abortion - Multiple births - Still or livebirth(s) - Birth defects			X	
*Newborn data ⁵ - Gestational age - Birthweight - APGAR score - HIV status				X

*Essential data

Footnotes:

1. ARV history to include start date, stop date and reasons for discontinuation
2. Any chronic disease diagnosis before pregnancy (if possible year of diagnosis), other co-morbidities diagnosed before pregnancy (for example cervical dysplasia, NAD cancers, co-infections).
3. Ideal time points for this data: at pregnancy start, prior to starting DTG treatment, every 3 months during pregnancy
4. Additionally, HIV RNA data to be collected at time of DTG discontinuation
5. Within 6 months of birth
6. Within 3-12 months of giving birth

Point of DTG exposure to be calculated in-house

13.2. APPENDIX 2: DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS GRADING SCALES

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

**Corrected Version 2.1
July 2017**

**Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services**

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Glossary and Acronyms

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 (<i>serum glutamic pyruvic transaminase</i>)
ANC	Absolute neutrophil count
AST(SGOT)	Aspartate aminotransferase (<i>serum glutamic-oxaloacetic transaminase</i>)
AV	Atrioventricular
Basic Self-care Functions	<u>Adult</u> Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. <u>Young Children</u> 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, then 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 30year 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 non-invasive 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 (e.g., 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.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immunoglobulin
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 (i.e, 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: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> 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 otherS 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 DAIDS-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 (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

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 (e.g., 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

Instructions for Use

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 (i.e., 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.

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 causing 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) <i>Specify type, if applicable</i>	No symptoms <u>AND</u> No intervention indicated	No symptoms <u>AND</u> Non-urgent intervention indicated	Non-life-threatening symptoms <u>AND</u> Non-urgent intervention indicated	Life-threatening arrhythmia <u>OR</u> Urgent intervention indicated
Blood Pressure Abnormalities ¹ <i>Hypertension (with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age</i>	140 to < 160 mmHg systolic <u>OR</u> 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic <u>OR</u> ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic <u>OR</u> ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) <u>OR</u> Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95 th to < 99 th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99 th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) <u>OR</u> Hospitalization indicated
<i>Hypotension</i>	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms <u>AND</u> IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction <i>Report only one</i>	NA	NA	New symptoms with ischemia (stable angina) <u>OR</u> New testing consistent with ischemia	Unstable angina <u>OR</u> Acute myocardial infarction
Heart Failure	No symptoms <u>AND</u> Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) <u>OR</u> Intervention indicated (e.g., oxygen)	Life-threatening consequences <u>OR</u> Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

¹ 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.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms <u>AND</u> No transfusion indicated	Symptoms <u>AND</u> Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension <u>OR</u> Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block <i>Report only one</i> <i>> 16 years of age</i>	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds <u>OR</u> Type I 2 nd degree AV block	Type II 2 nd degree AV block <u>OR</u> Ventricular pause ≥ 3.0 seconds	Complete AV block
<i>≤ 16 years of age</i>	1 st degree AV block (PR interval $>$ normal for age and rate)	Type I 2 nd degree AV block	Type II 2 nd degree AV block <u>OR</u> Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval²	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds <u>OR</u> ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism <i>Report only one</i>	NA	Symptoms <u>AND</u> No intervention indicated	Symptoms <u>AND</u> Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

² 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 <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> 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 (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., 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
Pruritus ³ (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
Rash <i>Specify type, if applicable</i>	Localized rash	Diffuse rash <u>OR</u> Target lesions	Diffuse rash <u>AND</u> Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions <u>OR</u> Ulceration of mucous membrane involving two or more distinct mucosal sites <u>OR</u> Stevens-Johnson syndrome <u>OR</u> Toxic epidermal necrolysis

³For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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 <u>OR</u> Modification of current medication regimen	Uncontrolled despite treatment modification <u>OR</u> Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes <u>AND</u> Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms <u>AND</u> Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities <u>OR</u> Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities <u>OR</u> Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms <u>AND</u> Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities <u>OR</u> Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities <u>OR</u> Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy⁴	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

⁴ Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Lipohypertrophy ⁵	Detectable by study participant, caregiver, or physician <u>AND</u> Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection <u>AND</u> Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

⁵ 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 associated with significant weight loss	Life-threatening consequences <u>OR</u> Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms <u>AND</u> Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension <i>Report only one</i>	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 <u>AND</u> Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea <i>≥ 1 year of age</i>	Transient or intermittent episodes of unformed stools <u>OR</u> Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools <u>OR</u> Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period <u>OR</u> IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
<i>< 1 year of age</i>	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools <u>OR</u> Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia <i>Report only one and specify location</i>	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 (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Mucositis or Stomatitis <i>Report only one and specify location</i>	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations <u>OR</u> Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) <u>OR</u> Tissue necrosis <u>OR</u> Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent <u>AND</u> 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 <u>OR</u> Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., 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 <u>OR</u> Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities <u>OR</u> Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent <u>AND</u> No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension <u>OR</u> Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., 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 <u>AND</u> No operative intervention indicated	Bone pain with radiographic findings <u>OR</u> Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia ⁶ ≥ 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 ⁶ ≥ 30 years of age	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

⁶BMD 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 (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see <i>Cognitive, Behavioral, or Attentional Disturbance</i> 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 <u>OR</u> Obtundation <u>OR</u> Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities <u>OR</u> 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 Disturbance (includes dementia and attention deficit disorder) <i>Specify type, if applicable</i>	Disability causing no or minimal interference with usual social & functional activities <u>OR</u> Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities <u>OR</u> Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities <u>OR</u> Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions <u>OR</u> Institutionalization indicated
Developmental Delay <i>< 18 years of age</i> <i>Specify type, if applicable</i>	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
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 <u>OR</u> Hospitalization indicated <u>OR</u> Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) <i>Specify type, if applicable</i>	Minimal muscle weakness causing no or minimal interference with usual social & functional activities <u>OR</u> 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 perform basic self-care functions <u>OR</u> Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) <i>Specify type, if applicable</i>	Minimal paresthesia causing no or minimal interference with usual social & functional activities <u>OR</u> 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 <i>New Onset Seizure</i> ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) <u>OR</u> Difficult to control (e.g., 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 <u>OR</u> > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) <u>OR</u> Difficult to control (e.g., refractory epilepsy)
<i>Pre-existing Seizure</i>	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) <u>OR</u> Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness <u>AND</u> 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) <i>Report only one</i>	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 ⁷ (report using mother's participant ID) <i>Report only one</i>	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

⁷ 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) <i>Specify disorder</i>	Symptoms with intervention not indicated <u>OR</u> Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated <u>OR</u> Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated <u>OR</u> Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others <u>OR</u> Acute psychosis <u>OR</u> Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt <i>Report only one</i>	Preoccupied with thoughts of death <u>AND</u> No wish to kill oneself	Preoccupied with thoughts of death <u>AND</u> 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 <u>OR</u> 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 $< 80\%$ <u>OR</u> Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to $< 70\%$ <u>OR</u> Symptoms with intervention indicated <u>OR</u> Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to $< 50\%$ <u>OR</u> Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow $< 25\%$ <u>OR</u> Life-threatening respiratory or hemodynamic compromise <u>OR</u> Intubation
Dyspnea or Respiratory Distress <i>Report only one</i>	Dyspnea on exertion with no or minimal interference with usual social & functional activities <u>OR</u> Wheezing <u>OR</u> Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities <u>OR</u> Nasal flaring <u>OR</u> Intercostal retractions <u>OR</u> Pulse oximetry 90 to $< 95\%$	Dyspnea at rest causing inability to perform usual social & functional activities <u>OR</u> Pulse oximetry $< 90\%$	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Hearing Loss <i>≥ 12 years of age</i>	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) <u>OR</u> Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
<i>< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)</i>	> 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) <u>OR</u> 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 <u>AND</u> Detectable on examination	Anterior uveitis with symptoms <u>OR</u> Medical intervention indicated	Posterior or pan-uveitis <u>OR</u> 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
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference 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 <u>OR</u> Mild angioedema with no intervention indicated	Generalized urticaria <u>OR</u> Angioedema with intervention indicated <u>OR</u> Symptoms of mild bronchospasm	Acute anaphylaxis <u>OR</u> Life-threatening bronchospasm <u>OR</u> 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 Syndrome⁸	Mild signs and symptoms <u>AND</u> Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated <u>AND</u> Responds promptly to symptomatic treatment <u>OR</u> Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms <u>OR</u> Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise <i>Report only one</i>	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
Pain⁹ (not associated with study agent injections and not specified elsewhere) <i>Specify location</i>	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 <u>OR</u> Hospitalization indicated

⁸ Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

⁹ For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness ¹⁰	Mild signs and symptoms	Moderate signs and symptoms <u>AND</u> Intervention indicated (e.g., antihistamines)	Severe signs and symptoms <u>AND</u> Higher-level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight ¹¹ > 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 <u>OR</u> Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

¹⁰Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

¹¹WHO 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/forparticipants>5to19yearsageand
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 <i>Report only one</i>	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 <u>OR</u> Hospitalization indicated
Injection Site Erythema or Redness ¹² <i>Report only one</i> <i>> 15 years of age</i>	2.5 to < 5 cm in diameter <u>OR</u> 6.25 to < 25 cm ² surface area <u>AND</u> Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter <u>OR</u> ≥ 25 to < 100 cm ² surface area <u>OR</u> Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter <u>OR</u> ≥ 100 cm ² surface area <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage <u>OR</u> Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
<i>≤ 15 years of age</i>	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling <i>Report only one</i> <i>> 15 years of age</i>	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
<i>≤ 15 years of age</i>	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
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 <u>OR</u> Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

¹² Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values*

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Acidosis	NA	pH \geq 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	\geq 2.0 to < 3.0 \geq 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	\geq 10.0 x ULN
Alkalosis	NA	pH > ULN to \leq 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High <i>Report only one</i>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	\geq 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High <i>Report only one</i>	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	\geq 5.0 x ULN
AST or SGOT, High <i>Report only one</i>	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	\geq 10.0 x 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 <i>Direct Bilirubin¹³, High</i> <i>> 28 days of age</i>	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
<i>\leq 28 days of age</i>	ULN to \leq 1 mg/dL	> 1 to \leq 1.5 mg/dL	> 1.5 to \leq 2 mg/dL	> 2 mg/dL
Total Bilirubin, High <i>> 28 days of age</i>	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	\geq 5.0 x ULN
<i>\leq 28 days of age</i>	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: 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.

¹³ 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.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
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
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	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
< 7 days of age	6.5 to < 7.5 1.63 to < 1.88	6.0 to < 6.5 1.50 to < 1.63	5.50 to < 6.0 1.38 to < 1.50	< 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 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance ¹⁴ or eGFR, Low *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m ² OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m ² OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m ² OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; mmol/L) Fasting, High	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Nonfasting, High	116 to 160 6.44 to < 8.89	> 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75

¹⁴Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73 m²). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Glucose, Low (mg/dL; mmol/L) <i>≥ 1 month of age</i>	55 to 64 3.05 to <3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
<i>< 1 month of age</i>	50 to 54 2.78 to < 3.00	40 to < 50 2.22 to < 2.78	30 to < 40 1.67 to < 2.22	< 30 < 1.67
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life- threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; mmol/L) Cholesterol, Fasting, High <i>≥ 18 years of age</i>	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA
<i>< 18 years of age</i>	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High <i>≥ 18 years of age</i>	130 to < 160 3.37 to < 4.12	160 to < 190 4.12 to < 4.90	≥ 190 ≥ 4.90	NA
<i>> 2 to < 18 years of age</i>	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
Magnesium¹⁵, 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) <i>> 14 years of age</i>	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
<i>1 to 14 years of age</i>	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
<i>< 1 year of age</i>	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

¹⁵ To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Sodium, High (mEq/L; mmol/L)	146 to < 150 <i>146 to < 150</i>	150 to < 154 <i>150 to < 154</i>	154 to < 160 <i>154 to < 160</i>	≥ 160 <i>≥160</i>
Sodium, Low (mEq/L; mmol/L)	130 to < 135 <i>130 to < 135</i>	125 to < 130 <i>125 to < 130</i>	121 to < 125 <i>121 to < 125</i>	≤ 120 <i>≤120</i>
Uric Acid, High (mg/dL; mmol/L)	7.5 to < 10.0 <i>0.45 to < 0.59</i>	10.0 to < 12.0 <i>0.59 to < 0.71</i>	12.0 to < 15.0 <i>0.71 to < 0.89</i>	≥ 15.0 <i>≥ 0.89</i>

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 x 10 ⁹ to < 0.650 x 10 ⁹	500 to < 600 0.500 x 10 ⁹ to < 0.600 x 10 ⁹	350 to < 500 0.350 x 10 ⁹ to < 0.500 x 10 ⁹	< 350 < 0.350 x 10 ⁹
Absolute Neutrophil Count (ANC), Low (cells/mm ³ ; cells/L) > 7 days of age	800 to 1,000 0.800 x 10 ⁹ to 1.000 x 10 ⁹	600 to 799 0.600 x 10 ⁹ to 0.799 x 10 ⁹	400 to 599 0.400 x 10 ⁹ to 0.599 x 10 ⁹	< 400 < 0.400 x 10 ⁹
2 to 7 days of age	1,250 to 1,500 1.250 x 10 ⁹ to 1.500 x 10 ⁹	1,000 to 1,249 1.000 x 10 ⁹ to 1.249 x 10 ⁹	750 to 999 0.750 x 10 ⁹ to 0.999 x 10 ⁹	< 750 < 0.750 x 10 ⁹
≤ 1 day of age	4,000 to 5,000 4.000 x 10 ⁹ to 5.000 x 10 ⁹	3,000 to 3,999 3.000 x 10 ⁹ to 3.999 x 10 ⁹	1,500 to 2,999 1.500 x 10 ⁹ to 2.999 x 10 ⁹	< 1,500 < 1.500 x 10 ⁹
Fibrinogen, Decreased (mg/dL; g/L)	100 to < 200 1.00 to < 2.00 OR 0.75 to < 1.00 x LLN	75 to < 100 0.75 to < 1.00 OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 0.50 to < 0.75 OR 0.25 to < 0.50 x LLN	< 50 < 0.50 OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin¹⁶, Low (g/dL; mmol/L) ¹⁷ ≥ 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 (female only)	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

¹⁶ 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 (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

¹⁷ 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.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
<i>57 days of age to < 13 years of age (male and female)</i>	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
<i>36 to 56 days of age (male and female)</i>	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
<i>22 to 35 days of age (male and female)</i>	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
<i>8 to ≤ 21 days of age (male and female)</i>	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
<i>≤ 7 days of age (male and female)</i>	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 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x 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 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm ³ ; cells/L)	100,000 to < 125,000 $100,000 \times 10^9$ to < $125,000 \times 10^9$	50,000 to < 100,000 $50,000 \times 10^9$ to < $100,000 \times 10^9$	25,000 to < 50,000 $25,000 \times 10^9$ to < $50,000 \times 10^9$	< 25,000 < $25,000 \times 10^9$
PT, High (not on anticoagulation therapy)	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm ³ ; cells/L)				
<i>> 7 days of age</i>	2,000 to 2,499 $2,000 \times 10^9$ to $2,499 \times 10^9$	1,500 to 1,999 $1,500 \times 10^9$ to $1,999 \times 10^9$	1,000 to 1,499 $1,000 \times 10^9$ to $1,499 \times 10^9$	< 1,000 < $1,000 \times 10^9$
<i>≤ 7 days of age</i>	5,500 to 6,999 $5,500 \times 10^9$ to $6,999 \times 10^9$	4,000 to 5,499 $4,000 \times 10^9$ to $5,499 \times 10^9$	2,500 to 3,999 $2,500 \times 10^9$ to $3,999 \times 10^9$	< 2,500 < $2,500 \times 10^9$

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 <u>OR</u> with RBC casts <u>OR</u> Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.

Total Bilirubin Table for Term and Pre-term Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Total Bilirubin¹⁸, High (mg/dL; $\mu\text{mol/L}$) ¹⁹				
Term Neonate²⁰ < 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
7 to 28 days of age (breast feeding)	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 breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate²⁰ 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 (breast feeding)	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 breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

¹⁸Severity 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-off values for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

¹⁹ A laboratory value of 1 mg/dL is equivalent to 17.1 $\mu\text{mol/L}$.

²⁰ 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.