Protocol REP 301-LTF
Version 1.0 April 4, 2016

A long term follow-up study of patients from the REP 301 protocol

Sponsor:

Replicor Inc.
6100 Royalmount Avenue
Montreal, Quebec
Canada H4P 2R2

Conduct: This clinical trial is being conducted in accordance with International Conference of Harmonization guidelines on-Good Clinical Practice (GCP) and the ethical principles originated from the Declaration of Helsinki. It is confirmed that the Clinical Trial Protocol meets the applicable regulatory requirements applicable

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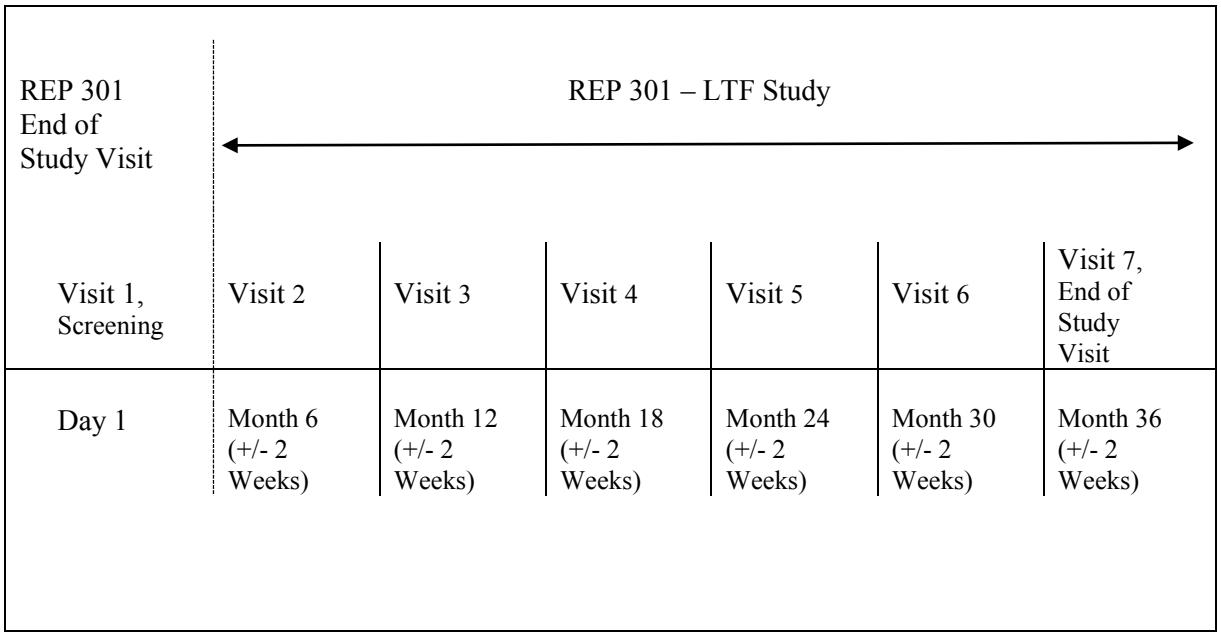
Figure 1. **Study Diagram**



LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
anti-HBe	Hepatitis B e-antigen antibody
anti-HBs	Hepatitis B surface antigen antibody
anti-HDAg	Hepatitis D antigen antibody
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CRF	Case report form
CT	Computed tomography
CTA	Clinical trial agreement
DAIDS	The Division of AIDS table for grading the severity of adult and pediatric adverse events
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e- antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCO3	Bicarbonate

Term	Definition
HDAg	Hepatitis D antigen
HDV	Hepatitis D virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IU	International units
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
ml	Milliliter
PEG-IFN	Pegylated interferon alpha 2a
PI	Principle Investigator
PID	Patient identification number
PT	Prothrombin time
PPT	Partial prothrombin time
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
ULN	Upper limit of normal
WBC	White blood cell

PROTOCOL APPROVAL SIGNATURE PAGE

Sponsor:
All persons who made a significant contribution to the preparation of the trial protocol (protocol development committee) should sign this page.

I have read and understand the contents of the clinical protocol REP 301-LTF dated April 4, 2016 and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Principal Investigator is informed of all relevant information that becomes available during the conduct of this study.

It is confirmed that the clinical trial protocol, the Case Report Forms (CRFs) and annexes contain all the necessary information and provisions to conduct the trial, that the trial is being conducted and documented in full in accordance with this protocol, and that the legal provisions and agreements described above are met.

Signature _____ Date APRIL 4, 2016

Dr. Andrew Vaillant, PhD
Chief Scientific Officer, Replicor Inc.

Signature _____ Date April 4, 2016

Dr. Michel Bazinet, MD
Chief Executive Officer and Chief Medical Officer, Replicor Inc.

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of the clinical protocol REP 301-LTF dated April 4, 2016 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current GCP and applicable regulatory requirements.

Principle Investigator:

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Signature of Principal Investigator

20.04.2016

Date

1. RATIONALE

Previous clinical trials have demonstrated that REP 2139-Ca administration in patients with chronic HBV infection was associated with the reduction/clearance of serum HBsAg and HBV DNA, the appearance of anti-HBs in the blood and an improved response to immunotherapy. The REP 301 treatment protocol involved the treatment of patients with chronic HBV/HDV co-infection with two agents: REP 2139-Ca and PEG-IFN. In this protocol, similar reduction/clearance of serum HBsAg and improved response to immunotherapy were observed in addition to clearance of serum HDV RNA, which is currently maintained in 12 patients (please refer to the current version of the REP 2139-Ca investigator brochure). The current REP 301protocol is designed to include a 24 weeks follow-up period after treatment, however given the strong antiviral response against HBV and HDV infection in these patients, it is now important to extend the follow-up period in these patients to monitor over a longer period after treatment the safety and efficacy combined REP 2139-Ca/PEG-IFN treatment in patients in the REP 301 protocol.

2. OBJECTIVES

Primary objective:

To address the long term safety of exposure to treatment with REP 2139-Ca and PEG-IFN in the REP 301 protocol.

Secondary objective:

To monitor the levels of serum HBsAg, serum anti-HBsAg, HBV DNA and HDV RNA in patients completing the REP 301 protocol.

3. ENDPOINTS

Primary endpoint:

- The proportion of patients with emergent lab test abnormalities, adverse events (AEs) or serious AEs (SAEs).
- The proportion of patients requiring concomitant therapy as a result of AEs

Secondary endpoints:

- Proportion of patients who maintain serum HBsAg < 1 IU/ml.
- Proportion of subjects who maintain anti-HBs titers above 10 mIU/ml
- Proportion of patients who maintain serum HBV DNA < 10 IU / ml
- Proportion of patients who maintain undetectable serum HDV RNA (target not detected).

4. STUDY DESIGN

The REP 301-LTF is a long-term follow-up, non-blinded study of patients from the REP 301 protocol. In this study, all eligible patients from the REP 301 protocol will have their follow-up evaluation extended for an additional 3 years, consisting of 6 visits scheduled every 6 months following the last follow-up visit scheduled in the REP 301 protocol. During each

visit a physical examination and documentation of any symptoms, experiences will be conducted as well as blood tests for safety and virology as described below.

This study will examine the long term safety effects in patients who have completed of treatment exposure in the REP 301 trial (REP 2139-Ca therapy for 30 weeks and PEG-IFN taken for 48 weeks with a 15 week overlap in combination) and the duration of suppression of serum HBV and HDV viremia observed in the REP 301 protocol. This requires that subjects have completed antiviral treatment in the REP 301 protocol and are not immediately transitioned to further antiviral treatment unless necessary.

Only those patients from the REP 301 protocol who are meeting the study eligibility criteria for the REP 310-LTF protocol will be enrolled in this long tern follow-up study. It is expected that all subjects who are on study will complete the protocol-defined durations for follow-up assessments.

It is expected that all subjects who are on study will complete the protocol-defined durations for follow-up assessments. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

The total duration of this study for each subject is 3 years. If a subject is withdrawn before completing the study, the reason for withdrawal must be recorded on the appropriate CRF page. Subjects who withdraw from the study will not be replaced.

Study Stopping rules:

There will be no study stopping. If PI cannot perform due to any reason, he will be replaced by another qualified physician. Due to its nature, the study shall be stopped only in the case of retirement of the PI where an alternate to the PI cannot be arranged.

Individual Stopping Rules:

Individuals may be stopped in the protocol if they withdraw consent for any study procedures or lose the ability to consent freely. If a subject is withdrawn before completing the study, the reason for withdrawal must be recorded on the appropriate CRF page.

5. STUDY POPULATION

For entry into the study, the following criteria must be met. There will be no randomization. Maximum 11 subjects will be enrolled into this study.

Inclusion Criteria

1) Signed written informed consent
Freely given informed consent must be obtained from subjects prior to clinical trial participation including informed consent for any screening procedures conducted to establish patient eligibility for the study.

2) Target Population

Successfully enrolled into the REP 301 protocol and completed all treatment and follow-up visits.

Exclusion Criteria

1) Any patients not enrolled in the REP 301 protocol or not successfully completing all treatment and follow-up visits in the REP 301 protocol
2) A history of alcohol abuse within the last year as defined using DSM IV criteria (Appendix 1)
3) The use of illicit drugs within the past two years as defined using DSM IV criteria (Appendix 1)
4) Inability to provide informed consent
5) Inability or unwillingness to provide blood samples

The following restrictions apply at all times:

1) Any antiviral medications with known antiviral effect against HBV or HDV are prohibited during the observation period except in the case of significant viral rebound of HBV or HDV infection. Other antiviral medications should not be used during this study unless approved by Replicor.
2) Long-term treatment ($\geq$ 2 weeks) with agents that are immunosuppressive or have a high risk for nephrotoxicity or hepatotoxicity.
3) Any prescription or herbal product which is not prescribed by the investigator or licensed physician for treatment of a specific clinical condition is prohibited.

Assessment of concomitant medications will be performed at each visit.

6. SCHEDULED ASSESSMENTS AND PROCEDURES

Subjects will be contacted and informed consent obtained according to routine procedures. All assessments (including laboratory assessment) made as part of end of study for REP 301 study and height measurement made as part of REP 301 study do not have to be repeated but can be used to include the subject in this study. Hence no extra examination or blood samples is necessary if the subject has performed the end of study assessment in the REP 301 protocol and switches over into this protocol. Informed consent should be obtained prior to the end of study visit in the prior study. Assessments will be performed according to table 1 below.

Table 1. Schedule of Assessments and Procedures for each visit:

Procedure / Test	**Frequency**
Inclusion and exclusion Criteria	Screening visit
Medical history	Taken from prior study
Vital signs[1]	Every visit
Physical examination	Every visit
Recording of AEs	Every visit
Verification of prior / concomitant medications[2]	Every visit
ECG	Every visit
Ultrasound	Every visit
Fibromax/Fibroscan	Every visit
HBV DNA/HDV RNA viral load	Every visit
HBsAg	Every visit
Anti-HBs/anti-HDAg	Every visit
HBeAg/anti-HBeAg	Every visit
ALT/AST/alkaline phosphatase[3]	Every visit
GGT	Every visit
Total bilirubin[4]	Every visit
Creatinine	Every visit
Biochemistry[5]	Every visit
Urinalysis	Every visit
Electrolytes[6]	Every visit
Hematology[7]	Every visit
INR/PTT/aPTT[8]	Every visit
Lipid profile[9]	Every visit
AFP	Every visit
ANA	Every visit
Frozen serum (4 X 1 cc aliquots)	Every visit

NOTES

1. Vital signs (seated blood pressure and heart rate), weight, and physical measurements and examinations must be performed at all study visits. Height measurement made as part of REP 301 study and weight measurement for calculation of BMI will be performed at each visit.
2. Any antiviral medications with known antiviral effect against HBV or HDV are prohibited during the observation period. Other antiviral medications should not be used during this study unless approved by Replicor. Long-term treatment (≥ 2 weeks) with agents that are immunosuppressive or have a high risk for nephrotoxicity or hepatotoxicity .Any prescription or herbal product which is not prescribed by the investigator or licensed physician for treatment of a specific clinical condition is prohibited.
3. Reflex to GGT if alkaline phosphatase ≥ 3X ULN
4. Reflex to direct bilirubin if abnormal; reflex to GGT if bilirubin ≥ 2X ULN
5. Albumin, globulin, total protein, LDH, BUN, phosphate, uric acid, fasting glucose, HbA1c
6. Na, HCO3-, K, Cl, Mg, Ca
7. RBC, WBC (count with differential), reticulocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width, platelet count, mean platelet volume, neutrophils, lymphocytes, monocytes, eosinophils, basophils.
8. INR, PT (reflex to PTT if≥ 2x PTT elevation), aPTT
9. Triglycerides, total cholesterol, HDL, LDL (all fasted)

Day 1 of the conduct of this study is last follow up visit (follow up week 24) in the REP 301 protocol. The last day of this study is the day the last patient finishes their last follow-up visit.

Each enrolled patient will be called in for an assessment every 6 months following the date of the Week 24 follow up visit in the REP 301 protocol for a period of 3 years (6 visits in total). The actual date of each visit can be adjusted by up to two weeks before or after the scheduled date of the visit in order to accommodate the patient's availability. Data evaluation will proceed real time as safety and efficacy data become available. After the last patient has

finished his follow up, the data analysis will be conducted within 6 months and final report will be submitted.

Medical History

Medical history within 5 years prior to Day 1 of the study will be recorded.

Laboratory Assessments

The assessments listed above will be analyzed by a central laboratory. Only data for the procedures and assessments specified in this protocol should be either recorded on the laboratory pages of the CRF as agreed upon between the investigator and Replicor. (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Additional procedures and assessments may be performed as part of the subject's standard medical care.

The Abbott Architect assay for HBsAg is a chemiluminescent microparticle immunoassay approved in Europe for the detection and quantitation of HBsAg. It is internally calibrated using the World Health Organization standard for HBsAg and measures HBsAg concentrations within the range of 0.05 to 250 IU/mL. The manufacturer recommends a 1:500 dilution of the test samples. Samples with HBsAg levels above or below this range require a lower or greater dilution in the manufacturer's diluent to bring them into the range of the calibration curve. The lower limit of detection of this assay is 0.05 IU/mL.

The Abbott Architect anti-HBs assay determines the concentration of antibody to hepatitis B surface antigen (anti-HBs) present in human serum and plasma. Samples with anti-HBs concentration less than 10.0 mIU/mL are considered non-protective by the anti-HBs assay. Samples with anti-HBs concentrations greater than or equal to 10.0 mIU/mL are considered protective.

Immunological Assessment

Immunological profile will include anti-nuclear antibody (ANA) at every visit.

Hematology Laboratory Assessments

Hematology laboratory including RBC count, hemoglobin, hematocrit, WBC count and differential (including ANC), reticulocyte count, mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution, width and platelet count, mean platelet volume, neutrophils, lymphocytes, monocytes, eosinophils, basophils will be collected at the visits as outlined above (or at the early termination visit) and at any unscheduled visit (only if clinically indicated).

Chemistry Laboratory Assessments Sodium, potassium, chloride, HCO_3, phosphate, calcium, magnesium, blood urea nitrogen (BUN), creatinine, glucose, HbA1c, albumin, globulin, total protein, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma- glutamyl transferase (GGT), uric acid, triglycerides (fasting), total cholesterol (fasting), HDL (fasting), LDL (fasting) will be collected at the visits outlined above (or at the early termination visit) and at any unscheduled visits (only if clinically indicated).

.Patients are required to fast after supper form the previous evening until completion of the blood test during the scheduled visit.

Fibromax

FibroMAX® is the combination of up to 5 non-invasive liver tests: FibroTest® diagnoses hepatic fibrosis, ActiTest® assesses viral necro-inflammatory activity, SteatoTest® diagnoses hepatic steatosis (otherwise known as 'fatty liver') - the most common cause of ALT and GGT abnormalities, ActiTest® assesses viral necro-inflammatory activity, AshTest® diagnoses severe alcoholic steatohepatitis (ASH) in excessive drinkers, NashTest® diagnoses non-alcoholic steatohepatitis (NASH) and includes 10 serum markers with the age, sex, height and weight of the patient: alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, ALT, AST, total cholesterol, triglycerides, fasting blood glucose.

Coagulation Profile

Coagulation profile including prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) will be collected at the visits as outlined above (or at the early termination visit) and at any unscheduled visits (only if clinically indicated).

HCC Assessment

Sampling for alpha-fetoprotein (AFP) will be performed at every visit

Serum Frozen Samples

The collected serum sample should be aliquoted into 4 eppendorf tubes™, 1 mL in each tube. Tubes should be frozen at -20˚C and retained at the refrigerator with regular temperature monitoring. Additional information on frozen samples and their storage will be provided in the Lab Manual.

Urinalysis

Urinalysis including specific gravity, pH, glucose, protein, ketones, nitrites, WBC and RBC will be performed at the visits as outlined above (or at the early termination visit) and at any unscheduled visits (only if clinically indicated). Microscopy will only be performed if any clinically significant abnormalities are observed in urinalysis.

Adverse Event Assessments

Subjects will be closely monitored throughout the study for AEs. AEs will be recorded and all study drug-related AEs considered related to previous treatment exposure in the REP 301 and persistent until EOS in the REP 301 protocol will be recorded as AEs in the REP 301-LTF study and will be followed until resolution or stabilization.

Vital Signs and Physical Examinations

Vital signs (seated blood pressure and heart rate), weight, and physical measurements and examinations must be performed at all study visits. Height and weight measurements will be

used for calculation of BMI at each visit. A full physical examination will be performed at each visit.
Liver assessment will include scheduled ultrasound, FibroMax and Fibroscan evaluations scheduled as described above.

Electrocardiogram (ECG)

An ECG performed while the subject is resting in a supine position will be recorded at study visits outlined above. The ECG should be recorded after the subject has been supine for at least 5 minutes.

Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to Replicor on a CRF. Additional procedures and assessments may be performed as part of the subject's standard medical care; however, data for these assessments should remain in the subject's medical record. Analysis of all HBV/HDV serum virology and anti-HBs results will be used to assess key efficacy endpoints.

Safety Assessments

Analysis of laboratory results and AEs/SAEs from each follow-up visit will be used to assess safety.

Scheduled procedures should follow the order as listed in Table 1.

7. INVESTIGATIONAL PRODUCT

No investigational product will be given during this protocol.

8. RECORDING AND REPORTING ADVERSE EVENTS

An AE is defined as ongoing AE present at the last study visit from the REP 301 protocol, any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject who received an investigational product whether or not having a causal relationship with this previous treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the previous use of investigational product, whether or not considered related to the investigational product.

All pre-existing AEs will be considered related to treatment received in the REP 301 protocol. All newly emergent AEs occurring within 12 months after last dose of IMP in the REP 301 protocol (based on 48 weeks of treatment with Pegasys®) will be considered related to treatment received in the REP 301 protocol unless they can be explained by another, unrelated medical condition or if consistent with any new medications the patient may start taking during the REP 301-LTF protocol. In the latter case, the newly emergent AE may be attributed to the new medication.

For AEs determined related to treatment from the REP 301 protocol, the relationship of the AE to Pegasys® or REP 2139-Ca exposure in the REP 301 protocol will be determined by the physician.

For newly emergent AEs observed 12 months after the last dose of Pegasys®, the causal relationship can be one of the following:

Related: There is a reasonable causal relationship between drug administration and the AE. This may be related to Pegasys® or REP 2139-Ca from the REP 301 protocol or to new medication being administered in the REP 301-LTF protocol.

Not related: There is no reasonable causal relationship between drug administration and the AE.AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

Serious Adverse Events (SAEs)

SAE is any untoward medical occurrence that at any dose:

a) results in death
b) is life-threatening (defined as an event in which the subject 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)
c) requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below)
d) results in persistent or significant disability/incapacity
e) is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE. Although pregnancy of a subject's partner, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs in this clinical study:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery planned prior to signing consent.
- Admissions as per protocol for a planned medical/surgical procedure routine health assessment requiring admission for baseline/trending of health status medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Pregnancy of a subject/subject's partner

If following initiation of the study, it is discovered that a subject or partner of a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 months after product administration, the investigator must immediately notify Replicor Inc. of this event in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Report Form and reported to Replicor.

SAE Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs must be collected including those thought to be associated with protocol-specified procedures. The investigator should report any SAE that occurs after these time periods.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE report form.

SAEs must be reported to Replicor, within 24 hours. SAEs must be recorded on the SAE report form when using paper forms, the reports are to be transmitted via email or confirmed facsimile transmission (if email is not available) to:

SAE Email Address: mbazinet@replicor.com
availlant@replicor.com

SAE Facsimile Number: +1 (514) 496-9011

The original paper forms should remain on site.

SAE Telephone Contacts: Primary: +1 (514) 951-6123 (Dr. Michel Bazinet)
Alternative: +1 (514) 862-2271 (Dr. Andrew Vaillant)

If only limited information is initially available, follow-up reports are required.
Follow-up SAE reports should include the same investigator term(s) initially reported.

If an ongoing SAE changes in its intensity or relationship to drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Replicor using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

Nonserious AEs

A nonserious AE is an AE not classified as serious. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see above). All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE report form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

If grading of laboratory abnormalities is reported as AEs or SAEs, the Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs should be used (see Appendix 2).

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, X-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or SAE, as appropriate and reported accordingly.

9. DATA QUALITY ASSURANCE

Compliance with Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with the local competent authorities and Replicor.

An amendment should be considered in the case of:

- medical impacts of the investigational product on the patient safety
- new insights that reduce the validity of the study
- change of the leading investigator of the study

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

a) IRB/IEC for review and approval/favorable opinion
b) Replicor.
c) Regulatory authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Replicor.

If an amendment substantially alters the study design or increases the potential risk to the subject:
1. The consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval
2. The revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment
3. The new form must be used to obtain consent from new subjects prior to enrollment

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

Monitoring

The study monitor(s) must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator and verify that the facilities remain acceptable.

In addition, the study may be evaluated by internal auditors and government inspectors who must be have access to CRFs, source documents, other study files and study facilities. Audit reports will be kept confidential.

The investigator must notify Replicor promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Replicor.

Investigational Site Training

The contract research organization managing the study on behalf of Replicor will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to GCP, AE reporting, study details and procedure, CRFs, study documentation and informed consent.

Records

The investigator must retain all study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region. The investigator must retain all study records for at least 7 years after the approval of a marketing application in the Republic of Moldova, but no more than 15 years after the formal discontinuation of clinical development studies of the investigational product in Republic of Moldova.

The investigator must contact Replicor prior to destroying any records associated with the study. Replicor will notify the investigator when the study records are no longer needed. If PI

withdraws from the study, the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer should be given in writing to Replicor.

Case Report Forms (CRF)

An investigator is required to prepare and maintain accurate case histories designed to record all observations and other data pertinent to the investigation on each individual Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements. The investigator should maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE CRFs, must be promptly reviewed, signed and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Clinical Study Report and Publications

The PI should sign the clinical study report.

The data collected during this study are confidential and proprietary to Replicor. Any publications or abstracts arising from this study require approval by Replicor prior to publication or presentation and must adhere to publication requirements as set forth in the Helsinki Declaration and the approved clinical trial agreement (CTA).

10. STASTICAL CONSIDERATIONS

Enrolled subjects are those who signed an informed consent form and were assigned a patient identification number (PID).Categorical variables will be summarized with counts and percents. Confidence intervals for difference in proportions will be based on the normal approximation with unpooled proportions used in the computation of the standard error of the difference. Continuous variables will be summarized with univariate statistics (eg, mean, median, standard error).

Baseline demography, HBV disease characteristics, and other baseline laboratory values will be tabulated by:

- Demographics: age, race, gender, ethnicity.
- Disease characteristics at the end of study visit in the REP 301 protocol: HBsAg level, HBV DNA/HDV RNA level, anti-HBs/anti-HDAg level and cirrhosis status.
- Physical measurements at inclusion: height, weight, BMI.
- Laboratory tests at baseline
- Prior medications

Longitudinal summaries of endpoints will use pre-defined visit week windows. Windows around planned measurement times will be constructed based on the midpoint between planned study visits.

Deaths will be listed for enrolled subjects without regard to study period. The frequencies of the following safety events will be summarized by:

- SAEs or AEs leading to discontinuation of observation.
- AEs (related and regardless of relationship to study) by intensity.
- Emergent laboratory abnormalities by toxicity grade.

The investigators will determine the intensity of AEs and the relationship of AEs to therapy. The investigators' terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at Replicor. AEs will be presented by system organ class and preferred term. If a subject had an AE with different intensities over time, then only the greatest intensity will be reported for a study period.

Laboratory toxicities will be graded according to the Division of AIDS (DAIDS) of the US National Institutes of Health table for grading the severity of adverse experiences (2004) (Appendix 2). The laboratory value during the study period with the highest toxicity grade will be reported for each test. Emergent laboratory abnormalities are those with highest toxicity grade greater than the baseline toxicity grade. Levels and changes in select laboratory tests over time will be summarized for subjects using observed values. Analyses of serum viremia will be based on HBsAg, anti-HBs, anti-HDAg, HBV DNA and HDV RNA measurements.
Details of the analyses will be provided in the Statistical Analysis Plan.

11. ETHICAL AND REGULATORY CONSIDERATIONS

Good Clinical Practice (GCP)

This study will be conducted in accordance with GCP, as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and as well as other valid national regulations.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. All potential serious breaches must be reported to Replicor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training and experience to perform their respective tasks.

Institutional Review Board/Independent Ethics Committee

Before study initiation the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form and any other written information to be provided to subjects. The investigator should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. In situations where consent cannot be given by subjects, they will not be included in the study. Each investigator will be provided with an appropriate sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented. The confidentiality of records that could identify subjects must be protected respecting the privacy and confidentiality rules applicable to regulatory requirements and the subjects' signed informed consent document. The consent form must also include a statement that Replicor and regulatory authorities have direct access to subject records. Subjects unable to give their written consent will not be included in the study. The rights, safety and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

12. ADRESSES/LIABILITY

Sponsor:

Replicor Inc.

6100 Royalmount Avenue, Suite D-101
H4P 2R2 Montreal, Quebec
Canada

Principal Investigator:

Dr. Victor Pântea
Infectious Diseases Department, State University of Medicine and Pharmacy
(n.a. Nicolae Testemitanu)
Infectious Clinical Hospital (n.a. Toma Ciorba)
Department of Infectious Diseases
Bul. Stefan cel Mare 163, 2004,
Chisinau, Republic of Moldova

13. ADMINISTRATIVE PROCEDURES

Legal regulations

This clinical trial will be conducted according to the Declaration of Helsinki and the regulations of the Republic Moldova in its valid form as well as the ICH-GCP guidelines and other valid national regulations.

Organizational arrangements/ investigational meetings

All PIs and their assistant personnel which is involved in the study will meet before the initiation of the study. The attendance is obligatory. In this meeting the clinical protocol and patient records will be discussed as well as the ethic, legal and scientific requirements for clinical studies according to the pharmaceutical products act and the ICH- recommendations for GCP. The meeting will be conducted for the coordination and standardization of the study procedures.

Data protection and medical confidentiality

In the context of this study all patient data in CRFs will be identified only with a patient number. The patients will be informed that the obtained data in the context of this study will be coded without referring to the patient's name (before submitting them elsewhere).

Case Report Forms (CRFs)
For each patient there will be a numerated CRF. All relevant data will be kept in the medical record and will be documented on the CRF. If corrections or complementation should be made in a way that the former entry is still readable. Additions and corrections should be signed and dated from the sub-investigators. Not self-explaining corrections have to be justified. Additions and corrections can be also conducted during the visit of a monitor. Additions and corrections can be conducted only through authorized people. These are apart from the principal, co- and sub-investigators study nurses or specifically trained medicinal personnel. All people that do corrections or additions should have signed in the list of the investigational file.

Retention of study records

After completion of the study and submission of the final report all study records will be archived. The PI is obliged to keep the investigational records as stipulated above.

14. OVERALL RISK-BENEFIT ASSESSMENT

All patients will have been off therapy for 24 weeks prior to the entry into this study. No investigational therapy will be given during this study. The only interventions planned are non-invasive patient exams and a blood tests but the use of marketed medication during the protocol may occur if required to manage AEs or rebound of HBV or HDV infection as stipulated above. As such there is no significant source of risk to the patients. The long term suppression of serum HBV and HDV viremia may be important indicators for the establishment of control and or elimination of infection and will be of benefit to the patient to understand their long term response to the treatment they received in the REP 301 protocol.

15. REFERENCES

1. ICH Harmonized Tripartite Guideline: Guideline for Good Clinical Practice: Recommended for Adoption at Step 4 of the ICH Process on 1 May 1996 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
2. ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting: Recommended for Adoption at Step 4 of the ICH Process on 27. October 1994 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
3. ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports: Recommended for Adoption at Step 4 of the ICH Process on 30 November 1995 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA..
4. ICH Harmonized Tripartite Guideline: General Considerations for Clinical Trials: Recommended for Adoption at Step 4 of the ICH Process on 17 July 1997 by the ICH Steering Committee This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
5. ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials: Recommended for Adoption at Step 4 of the ICH Process on 5 February 1998 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

16. APPENDIX 1 DSM IV: DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

Criteria for alcohol & substance abuse

1) A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

a) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

b) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

c) Recurrent substance-related legal problems (e.g., arrests for substance related disorderly conduct)

d) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

2) The symptoms have never met the criteria for Substance Dependence for this class of substance.

17. APPENDIX 2 DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

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II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	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 fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	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
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	**≥** 180 mmHg systolic OR **≥** 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
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 OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or 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				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	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 OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	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 OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	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
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
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

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	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 See also Arthralgia	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
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	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

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	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
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	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

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	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
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (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)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 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

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

Comment: Added ULN to Grade 1 parameter					
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low		1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
	Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high		5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low		3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high		146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low		130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)		NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).