CLINICAL STUDY PROTOCOL

Study Title:	A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, California 94404, USA
EudraCT No.:	Not applicable
Protocol ID:	GS-US-162-0112
Gilead Medical Monitor:	Name: Erin Quirk, M.D. Telephone: PPD Fax: PPD
CRO Medical Monitor:	Not applicable
Protocol Version/ Date:	Amendment 1: 24 July 2013 Original: 24 January 2005

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Dr,
Foster City, CA 94404, USA

Title of Study:	A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine
EudraCT Number:	Not applicable
Study Centers:	This study will be conducted at two study centers: PPD Perinatal HIV Research Unit PPD PPD Infectious Diseases Clinical Trial Unit PPD
Objective:	The objectives of this study are: • To provide current FTC-203 study participants in South Africa with continued access to the study drug, emtricitabine, following completion of the FTC-203 study. • To collect long-term safety information in subjects receiving emtricitabine in combination with other antiretroviral agents.
Study Design:	The fourth amendment to the FTC-203 protocol allowed subjects meeting predetermined virologic criteria to continue receiving emtricitabine beyond the Week 96 Visit until such time as emtricitabine is available via market distribution in the subject's country of residence. With the last subject completing the original 48-week study duration in May 2004, the decision has been made to close the FTC-203 study after the last subject completes the Week 96 visit. In those countries where regulatory approval for market distribution of emtricitabine has yet to be sought and/or is pending, alternative means to provide FTC-203 study participants with continued access to emtricitabine are being implemented. This open-label, non-randomized rollover protocol will provide those FTC-203 study participants enrolled at the two study centers in South Africa with continued access to the study drug,

	emtricitabine, following the completion of the FTC-203 study. Each eligible subject electing to participate in the rollover protocol will continue to receive emtricitabine, to be administered in combination with other antiretroviral medications, for as long as (s)he continues to meet the aforementioned virologic criteria. Emtricitabine will be provided by the Sponsor; all other antiretroviral medications will be sourced through a local commercial supplier and funded through a treatment grant program.
Number of Subjects Planned:	Enrollment will be limited to current FTC-203 study participants enrolled at the two study centers in South Africa. A total of 59 subjects were enrolled between the two study centers, representing the maximum possible enrollment in this protocol.
Target Population:	HIV-1 infected pediatric subjects currently enrolled in FTC-203 at the two study centers in South Africa who are eligible and who wish to continue to receive the study drug, emtricitabine, beyond completion of the FTC-203 study. Subjects must have completed at least 96 weeks on the FTC-203 study and will be required to complete the End-of-Study Visit for FTC-203 prior to transitioning into the rollover protocol.
Duration of Treatment:	Subjects participating in the rollover protocol will receive the study drug, emtricitabine, for as long as they continue to meet the following virologic criteria: • they have a plasma HIV-1 RNA viral load of ≤ 400 copies/mL, or • if the subject's plasma HIV-1 RNA viral load is > 400 copies/mL, their viral load is < 1.0 $\log_{10}$ above the nadir recorded after Week 8 of the FTC-203 study and there is reliable genotypic evidence showing a lack of resistance to emtricitabine, and until either: (1) the subject chooses to discontinue treatment of emtricitabine and withdraw from the rollover protocol; (2) the subject experiences a toxicity that necessitates the permanent discontinuation of emtricitabine, or (3) emtricitabine is approved for market distribution in the subject's country of residence.
Diagnosis and Main Eligibility Criteria:	Current FTC-203 study participants are eligible to participate in this rollover protocol if (1) they complete all End-of-Study Visit procedures for the FTC-203 study, and (2) either (a) they have a plasma HIV-1 RNA viral load of ≤ 400 copies/mL at the End-of-Study Visit, or (b) if the subject's plasma HIV-1 RNA viral load is > 400 copies/mL at the End-of-Study Visit, their viral load is < 1.0 $\log_{10}$ above the nadir recorded after Week 8 of the FTC-203 study and there is reliable genotypic evidence showing a lack of resistance to emtricitabine.

Study Procedures/ Frequency:	During the rollover protocol, the Investigator will manage each subject according to current "standard of care" practices at his (or her) institution, with the subject returning to the clinic approximately every 12 weeks for study visits (i.e., four visits per year). The Investigator may choose to have the subject return to the clinic on a more frequent basis as part of their standard of care, but these visits will be outside of the protocol-defined visit schedule. Data collection during the rollover protocol for safety purposes will be limited to the reporting of adverse events (AEs) that (1) meet the criteria for a serious adverse event (SAE), (2) result in permanent discontinuation of the study drug, emtricitabine, and/or (3) are associated with skin discoloration (hyperpigmentation). Information relating to the dispensing and accountability of the study drug will also be recorded. Non-serious AEs that do not result in the discontinuation of emtricitabine and/or are not associated with skin discoloration (hyperpigmentation), the results of routine clinical laboratory testing (hematology, clinical chemistry and urinalysis), immunological data (absolute and percent CD4+), pregnancy test results, and physical examination findings collected in the FTC-203 study will no longer be collected or recorded in the case report form (CRF), nor will the findings of any assessments done according to current standard of care practices be recorded in the CRF. HIV-1 RNA viral load levels will be assessed at each clinic visit to ensure continued subject eligibility, regarding the virologic criteria; however, these data will not be recorded in the CRF. Genotypic analysis may be required to determine whether a subject is eligible to participate in the rollover protocol at the End-of-Study Visit for FTC-203 or, after they have entered the rollover protocol, to determine whether the subject has failed the criteria for virologic success and should permanently discontinue treatment with the study drug, emtricitabine.
Test Product, Dose, and Mode of Administration:	Emtricitabine: 6 mg/kg once daily (QD), up to a maximum of 200 mg QD using the capsule formulation or up to a maximum of 240 mg QD using the oral solution formulation, with both formulations administered orally. Other antiretroviral medications will be administered at the dose or doses recommended by the manufacturer in the relevant product/package insert for the treatment of pediatric patients.

Reference Therapy, Dose, and Mode of Administration:	Not applicable.
Criteria for Evaluation:	
Safety:	SAEs, AEs leading to discontinuation of the study drug, emtricitabine, regardless of seriousness/severity and AEs associated with skin discoloration (hyperpigmentation) will be recorded in the CRF.
Efficacy:	Not applicable.
PK:	Not applicable.
Statistical Methods:	No statistical analyses are planned. Data listings will be generated for all data collected in the clinical database. Listings will include subject enrollment/disposition, demographics (from the FTC-203 clinical database), SAEs, AEs leading to permanent discontinuation of study drug, emtricitabine, AEs associated with skin discoloration (hyperpigmentation), and study drug dispensing/accountability. Tabular summaries will be prepared.

This study is being performed in compliance with the guideline of Good Clinical Practice (GCP) and all essential documents are being archived as required by regulatory authorities.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event (or experience)
ART	antiretroviral therapy
β-HCG	beta human chorionic gonadotropin
CFR	US Code of Federal Regulations
CRF	Case Report Form
DAIDS	Division of AIDS, NIAID
EU	European Union
EUDRA(CT)	European Union Drug Regulatory Authorities (Clinical Trials)
FDA	US Food and Drug Administration
FTC	emtricitabine (Emtriva®)
GCP	Good Clinical Practice (Guidelines)
GSI	Gilead Sciences, Inc.
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
NIAID	US National Institute of Allergy and Infectious Diseases
NRTI	nucleoside reverse transcriptase inhibitor
QD	quaque die (once daily)
RNA	ribonucleic acid
SAE	serious adverse event (or experience)
US(A)	United States (of America)

1. INTRODUCTION

1.1. Background

Emtricitabine (5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-[1,3]-oxathiolan-5-yl] cytosine, FTC) is a nucleoside reverse transcriptase inhibitor (NRTI) that has demonstrated potent and selective inhibition of the human immunodeficiency virus (HIV). In HIV-infected adults, emtricitabine is administered as a 200 mg once daily (QD) dose concurrently with other antiretroviral drugs. The 200 mg Emtriva® (emtricitabine) Capsule formulation was approved by the US Food and Drug Administration (FDA) for marketing on 2 July 2003. In the European Union (EU), marketing authorization was granted for both the 200 mg Emtriva® (emtricitabine) Capsule formulation and a 10 mg/mL Emtriva® (emtricitabine) Oral Solution formulation on 24 October 2003, with indications for the treatment of HIV infection concurrently with other antiretroviral drugs in both adult and pediatric patients. In pediatric patients, the recommended dose of emtricitabine is 6 mg/kg QD, up to a maximum of 200 mg QD when administered using the capsule formulation (for children weighing > 33 kg) or up to a maximum of 240 mg when administered using the oral solution formulation. Gilead Sciences, Inc. (GSI) continues to pursue applications for regulatory approval of emtricitabine in selected countries outside of the USA and EU.

1.2. Rationale for the Current Study

Study FTC-203 is an ongoing multi-center, open-label, non-randomized Phase 2 clinical study to evaluate the safety, antiretroviral activity and pharmacokinetics of emtricitabine in combination with other antiretroviral agents in pediatric HIV-infected patients. The study was designed to enroll approximately 60 to 120 HIV-1 infected, ART-naïve and ART-experienced, male and female pediatric patients between the ages of 3 months and 17 years, inclusive. A total of 116 patients with confirmed HIV-1 infection were actually enrolled in this study between 12 study centers located in the USA (8 centers), South Africa (2 centers), Mexico (1 center) and Panama (1 center). Twenty-two patients were enrolled in the USA, with 59 patients enrolled in South Africa, 6 patients enrolled in Mexico and 29 patients enrolled in Panama.

According to the original protocol, all patients were to be treated for an initial period of at least 48 weeks, providing (s)he did not meet the study drug discontinuation criteria. With the implementation of the third protocol amendment, the study duration was formally extended to 96 weeks, thereby allowing patients to continue receiving treatment for an additional 48 weeks providing they met and continued to meet one of the following virologic criteria:

- the patient's plasma HIV-1 RNA level was ≤ 400 copies/mL

  OR

- if the patient's plasma HIV-1 RNA level was > 400 copies/mL, the patient's plasma HIV-1 RNA level was < 1.0 $\log_{10}$ above the nadir recorded after Week 8 and there was reliable genotypic evidence showing a lack of viral resistance to emtricitabine.

With the implementation of the fourth protocol amendment, patients who continued to meet either of the above virologic criteria were allowed to continue receiving emtricitabine beyond Week 96 until such time as the drug is available via market distribution in the patient's country of residence. With the last patient completing the original 48-week study duration in May 2004, the decision has been made to close the FTC-203 study after the last patient completes his (or her) Week 96 visit. In those countries where regulatory approval for market distribution of emtricitabine has yet to be sought and/or is pending, alternative means to continue to provide FTC-203 study participants with access emtricitabine are being implemented. The purpose of the current protocol is to allow those patients in South Africa who are current FTC-203 study participants to continue to receive emtricitabine (either capsule or oral solution formulation) beyond completion of the FTC-203 study. Each eligible subject electing to participate in the rollover protocol will continue to receive emtricitabine, to be administered in combination with other antiretroviral medications, for as long as (s)he continues to meet the aforementioned virologic criteria.

2. OBJECTIVES

The objectives of this study are:

- To provide current FTC-203 study participants in South Africa with continued access to the study drug, emtricitabine, following completion of the FTC-203 study in both countries.

- To collect long-term safety information in subjects receiving emtricitabine in combination with other antiretroviral agents.

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is an open-label, non-randomized rollover protocol that will provide current FTC-203 study participants enrolled at the two study centers in South Africa with continued access to the study drug, emtricitabine, following completion of the FTC-203 study. A total of 59 subjects were enrolled in South Africa between the two study centers, representing the maximum possible enrollment in this protocol.

Each eligible subject electing to participate in the rollover protocol will continue to receive emtricitabine, in combination with other antiretroviral medications, for as long as they continue to meet the following virologic criteria:

- they have a plasma HIV-1 RNA viral load of ≤ 400 copies/mL, or
- if the subject's plasma HIV-1 RNA viral load is > 400 copies/mL, their viral load is < 1.0 $\log_{10}$ above the nadir recorded after Week 8 of the FTC-203 study and there is reliable genotypic evidence showing a lack of resistance to emtricitabine,

and until either: (1) the subject chooses to discontinue treatment of emtricitabine and withdraw from the rollover protocol; (2) the subject experiences a toxicity that necessitates the permanent discontinuation of emtricitabine, or (3) emtricitabine is approved for market distribution in the subject's country of residence.

Subjects must complete at least 96 weeks on the FTC-203 study and will be required to complete the End-of-Study Visit for FTC-203 before transitioning into the rollover protocol. During the rollover protocol, the Investigator will manage each subject according to current "standard of care" practices at his (or her) institution, with the subject returning to the clinic approximately every 12 weeks for study visits (*i.e.*, four times per year). The Investigator may choose to have the subject return to the clinic on a more frequent basis as part of their standard of care, but these visits will be outside of the protocol-defined visit schedule.

Data collection during the rollover protocol for safety purposes will be limited to the reporting of adverse events (AEs) that (1) meet the criteria for a serious adverse event (SAE), (2) result in permanent discontinuation of the study drug, emtricitabine, and/or (3) are associated with skin discoloration (hyperpigmentation) (see Section 7.8.1). Information relating to the dispensing and accountability of the study drug will also be recorded.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Enrollment will be limited to current FTC-203 study participants enrolled at the two study centers in South Africa. A total of 59 subjects were enrolled between the two study centers, representing the maximum possible enrollment in this protocol. Prospective subjects must complete at least 96 weeks on the FTC-203 study and will be required to complete the End-of-Study Visit for FTC-203 before transitioning into the rollover protocol. Prospective subjects must also meet the inclusion criteria described in Section 4.2 below.

4.2. Inclusion Criteria

To participate in the rollover protocol, each subject must meet *all* of the following inclusion criteria:

- Complete or have previously completed at least through the Week 96 Visit (*i.e.*, 96 weeks on study) for the FTC-203 study.
- Complete all End-of-Study Visit procedures for the FTC-203 study.
- Either (a) have a plasma HIV-1 RNA viral load of ≤ 400 copies/mL at the End-of-Study Visit for the FTC-203 study, or (b) if the subject's plasma HIV-1 RNA viral load at the End-of-Study Visit for FTC-203 study is > 400 copies/mL, their viral load is < 1.0 $\log_{10}$ above the nadir recorded after Week 8 of the FTC-203 study and there is reliable genotypic evidence showing a lack of resistance to emtricitabine.
- A parent or other legal guardian has provided written informed consent to the subject participating in the rollover protocol. As applicable, based on the subject's age and normal institution practice, the subject should additionally provide their written informed consent or assent to participate in the rollover protocol.
- If a female of childbearing potential has a negative serum beta-human chorionic gonadotropin (β-HCG) test at the End-of-Study Visit for the FTC-203 study.
- If sexually active (male and female) and/or of childbearing potential, be willing to use an effective method of contraception while enrolled in the study and for a period of at least 1 month after the last dose of emtricitabine. See Section 7.9.4 for more information on contraception and pregnancy.
- Male subjects must refrain from sperm donation from Day -1 through completion of the study and continuing for at least 90 days from the date of last dose of study drug.

- Have no medical condition or any other set of circumstances, which, in the opinion of the Investigator or Sponsor, means that it would not be in the best interests of the subject to participate in the rollover protocol and/or continue treatment with emtricitabine.

4.3. Exclusion Criteria

Not applicable.

5. STUDY DRUGS

Each eligible subject electing to participate in the rollover protocol will continue to receive emtricitabine, in combination with other antiretroviral medications. Emtricitabine will be provided by the Sponsor; all other antiretroviral medications will be sourced through a local commercial supplier and funded through a treatment grant program.

5.1. Randomization and Blinding

Not applicable; this is an open-label study.

5.2. Description and Handling of Emtricitabine

5.2.1. Formulation

Emtricitabine will be provided as a flavored, sweetened oral solution (10 mg/mL) and a solid medication, as 200 mg gelatin capsules.

Generic Name:	Emtricitabine (USAN-approved)
CAS Name:	(2R-*cis*)-4-amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxanthiolan-5-yl]-2 (1H)-pyrimidinone
CAS Number:	143491-57-0
IUPAC Name:	(2R,5S)-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
Other Names:	(-)-2',3'-dideoxy-5-fluoro-3'-thiacytidine FTC
Dosage Forms:	Oral solution; Capsule
Strength:	10 mg/mL; 200 mg

Additional information on the emtricitabine formulations can be found in the Investigator's Brochure (See the most recent edition of the Emtricitabine (FTC) Brochure).

5.2.2. Packaging and Labeling

Emtricitabine will be supplied by GSI from a central drug storage facility. Drug labels will reflect all necessary information required by the relevant regulatory authority(ies) and/or local laws governing the packaging and labeling of investigational medications.

5.2.3. Storage and Handling

Qualified personnel at each study center will dispense emtricitabine to subjects at each clinic visit. The Investigator (or designee) will need to monitor the supply of emtricitabine for each subject and order the drug as needed from the central drug storage facility. Once received by

the study center, emtricitabine must be accounted for in the drug accountability log provided by the Sponsor (or equivalent documentation). The log will include the date the medication is received at the study center, the date drug is dispensed to a subject, and the date any extra medication or empty bottles are returned to the study center by the subject. All unused emtricitabine must be returned to the Sponsor's designee at the end of the study.

Emtricitabine oral solution should be refrigerated at 2 to 8°C (36 to 46°F) until dispensed. Once dispensed to the subject, emtricitabine oral solution may be kept at room temperature up to 25°C (77°F) for ≤ 90 days. Emtricitabine capsules should be stored at 15 to 30°C (59 to 86°F). The storage conditions for emtricitabine may change during this protocol. If this occurs, revised instructions regarding the storage of emtricitabine will be provided.

Additional information regarding the storage and handling of emtricitabine capsules and oral solution can be found in the emtricitabine Investigator's Brochure (See most recent edition of the Emtricitabine (FTC) Brochure).

5.3. Dosage and Administration of Emtricitabine

The exact volume of solution/number of capsules of emtricitabine to be administered will be based on body weight at a dose of 6 mg/kg QD, with a maximum dose of 200 mg QD using the capsule formulation (for children weighing ≥ 33 kg) or a maximum dose of up to 240 mg QD using the oral solution formulation. The 6 mg/kg QD dose has been shown to achieve steady-state emtricitabine plasma concentration comparable to that observed in adults given the recommended 200 mg of emtricitabine QD using capsules {7438}.

For the purposes of determining the dose of emtricitabine to be administered, each subject's body weight (in kg) will be measured at each study visit (such data will not be recorded in the CRF). Older subjects should be weighed with only a minimum amount of clothing in place. Infants and toddlers using diapers should be weighed naked. Clinic visits are specified at 12-week intervals; however, it may be appropriate for subjects receiving emtricitabine oral solution to attend the clinic more frequently to be reweighed, to allow the dose of the emtricitabine oral solution (and, where appropriate, other antiretroviral medications) to be adjusted to reflect any change in their body weight. In this case, the exact visit schedule will be left to the Investigator's discretion, taking into account the age of the child and other relevant factors. Regardless, no more than a 60-day supply of the emtricitabine oral solution may be dispensed to any subject (or his/her family) who does not have the means to adequately refrigerate the drug at home, thereby necessitating more frequent visits by the subject to the clinic to resupply the drug.

Dosing tables for emtricitabine are provided in Appendix 1 to the protocol. These tables should be used to determine for each individual subject whether the child should receive capsules (body weight ≥ 33 kg) or oral solution and, if the latter, the volume of solution to be administered.

Each dose of emtricitabine should be administered all at once using means appropriate for the age of the subject. Sufficient water or other fluids should be offered to facilitate swallowing/washdown of emtricitabine, as necessary. Emtricitabine can be dosed without regard to food. It is recommended that the emtricitabine be given at the same time the subject takes his (or her) other antiretroviral medications. A subject who vomits within 30 minutes of taking his/her dose of emtricitabine should be re-dosed.

5.4. Prior and Concomitant Medications

Currently, no drugs are contraindicated for co-administration with emtricitabine. Investigators should refer to the product/package inserts of the other antiretroviral medications for contraindications related to their use.

6. STUDY PROCEDURES

6.1. Subject Enrollment and Treatment Assignment

Before enrolling in this study, subjects must have completed through at least 96 weeks on the FTC-203 study and complete the End-of-Study Visit procedures for FTC-203 (see Section 6.2.1 and Appendix 2 hereinafter for details). The subject's parent(s) or other legal guardian(s) must then provide written informed consent for him (or her) to participate in the rollover protocol. Where applicable, depending on the age of the subject and prevailing institution practice regarding consenting minors, consent or assent may also be obtained from the subject. Subjects who participate in this rollover protocol must meet the inclusion criteria detailed in Section 4.2. To ensure uninterrupted treatment with the study drug, emtricitabine, if there is a reasonable expectation that the subject will meet the virologic criteria set out in Section 3.1, based on the results of HIV-1 RNA viral load testing performed at previous FTC-203 clinic visits, the End-of-Study Visit for the FTC-203 study and the Baseline visit of the rollover protocol can and should be completed at the same clinic visit, with the subject receiving his first supply of emtricitabine through the rollover protocol at that visit.

6.2. Study Assessments

6.2.1. End-of-Study Visit (FTC-203)/Baseline Visit (GS-US-162-0112)

For the End-of-Study Visit for the FTC-203 study, the following procedures will be completed:

- Record height (or length) and body weight.
- Perform a physical examination.
- Obtain vital signs.
- Obtain blood and urine samples for the following laboratory evaluations: CD4+ cell count, plasma HIV-1 RNA level, plasma for storage, hematology, chemistry and urinalysis
- Female subjects of childbearing potential must have a urine pregnancy test performed. If the urine pregnancy test is positive, a serum β-HCG test should be performed and the GSI Medical Monitor contacted.
- Record HIV-1 related events, adverse events, and concomitant medications.
- Complete drug accountability, including ensuring that all previously unused FTC-203 study medications(s), *i.e.*, the study drug, emtricitabine, and, where applicable, the lopinavir-ritonavir and stavudine provided for ART-naïve subjects, is/are returned by the subject.

The following procedures will be completed as part of the Baseline Visit for the GS-US-162-0112 rollover protocol:

- Obtain written informed consent from parent or other legal guardian and, where applicable, the subject.
- Review inclusion criteria for the rollover protocol.
- Record height (or length) and body weight.
- Review adverse events.
- Complete drug accountability and provide a new supply of the study drug, emtricitabine for the rollover protocol.

Procedures required at both the End-of-Study Visit for FTC-203 and the Baseline Visit will not need to be repeated if done at the same clinic visit. However, information may need to be recorded in the CRFs of both studies.

Genotypic analysis may be performed for subjects to determine whether they are eligible to participate in the rollover protocol. If needed, genotypic analysis will be performed through the Clinical Virology group, GSI. As necessary, each study center should contact the GSI Clinical Program Manager responsible for the rollover protocol to request approval for genotypic analysis, as well as sample collection and shipping instructions to the GSI office.

6.2.2. Clinic Visits

During the rollover protocol, clinic visits will occur every 12 weeks. At each visit, the Investigator will manage each subject's care according to current "standard of care" practices at his (or her) institution, complete drug accountability and provide the subject with a new supply of emtricitabine. Each Subject will continue to receive the study drug, emtricitabine, for as long as they continue to meet the following virologic criteria, either:

- they have a plasma HIV-1 RNA viral load of ≤ 400 copies/mL, or
- if the subject's plasma HIV-1 RNA viral load is > 400 copies/mL, their viral load is < 1.0 $\log_{10}$ above the nadir recorded after Week 8 of the FTC-203 study and there is reliable genotypic evidence showing a lack of resistance to emtricitabine.

At each clinic visit, the Investigator (or designee) will measure the child's height (or length) and weight if the subject has not maintained the same height for three consecutive protocol visits (36 weeks), or if the height and weight are necessary to determine study drug dosage. The Investigator (or designee) will assess adverse events, but only those AEs that (1) meet the criteria for an SAE, (2) that result in permanent discontinuation of the study drug, emtricitabine, and/or (3) are associated with skin discoloration (hyperpigmentation) will be recorded in the subject's CRF. Non-serious AEs that do not result in the discontinuation of

emtricitabine and/or are not associated with skin discoloration (hyperpigmentation), the results of routine clinical laboratory testing (hematology, clinical chemistry and urinalysis), immunological data (absolute and percent CD4+), pregnancy test results, and physical examination findings collected in the FTC-203 study will no longer be collected or recorded in their CRF, nor will the findings of any assessments done according to current standard of care practices be recorded in the CRF. Information relating to the dispensing and accountability of the study drug will be recorded in the CRF.

HIV-1 RNA viral load levels will be assessed at each clinic visit to ensure continued subject eligibility, regarding the virologic criteria; however, these data will not be recorded in the CRF. Genotypic analysis may be required to determine whether a subject is eligible to participate in the rollover protocol at the End-of-Study Visit for FTC-203 or after they have entered the rollover protocol to determine whether the subject has failed the criteria for virologic success and should permanently discontinue treatment with the study drug, emtricitabine.

Further study visits will be scheduled at approximately 12-week intervals (*i.e.*, four times per year) for as long as the subject continues to meet the virologic criteria until such time as: (1) the subject chooses to withdraw from the rollover protocol and discontinue treatment of emtricitabine, (2) the subject experiences a toxicity that necessitates the permanent discontinuation of emtricitabine, or (3) emtricitabine is approved for market distribution in the subject's country of residence. The Investigator may choose to have the subject return to the clinic on a more frequent basis as part of their standard of care, but these visits will be outside of the protocol-defined study visit schedule. Younger subjects receiving emtricitabine oral solution may need to attend the clinic more frequently than every 12 weeks to be reweighed to allow the dose of the emtricitabine oral solution (and, where appropriate, other antiretroviral medications) to be adjusted to reflect any change in their body weight. In addition, for subjects receiving emtricitabine oral solution, if the subject does not have the means to adequately refrigerate the solution at home, it will also be necessary for him (or her) to make more frequent visits to the clinic to obtain fresh supplies of drug. In the event that a more frequent visit schedule is required, only drug dispensing and accountability information will be recorded in the CRF at those visits.

6.3. Assessments for Premature Discontinuation From Study

If a subject discontinues the study drug, emtricitabine, regardless of reason, the Investigator should assess all reported AEs and complete drug accountability. Any AE(s) that led to the permanent discontinuation of study drug should be recorded in the CRF. The subject must return all unused study drug to the study center. The Investigator (or designee) will measure the child's height (or length) and weight.

6.4. Criteria for Suspension of Study Drug

Subjects who do not maintain plasma HIV-1 RNA levels as outlined in Section 6.2.2 above must be discontinued from study drug. Furthermore, the study drug, emtricitabine, may be discontinued in the following instances:

- Upon approval for market distribution in South Africa (and the subject has means to access the drug).

- Unacceptable emtricitabine-related toxicity necessitating the permanent discontinuation of study drug. Brief (generally ≤ 14 days) interruptions in treatment are permitted, *e.g.*, to manage a newly emergent toxicity. Longer (> 14 days) interruptions are permitted only with the approval of the GSI Medical Monitor and will be decided on a case-by-case basis.

- Subject request to discontinue for any reason.

- Subject non-compliance (in the judgment of the Investigator or Sponsor).

- Subject pregnancy.

- In the judgment of the Investigator or Sponsor, it is not considered to be in the subject's best interest (for whatever reason) to continue in the rollover protocol.

- Discontinuation of the rollover protocol at the request of GSI, applicable regulatory agency(ies) or IEC.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (*e.g.*, invasive procedures such as venipuncture, biopsy, *etc.*). Pre-existing events, which increase in severity or change in nature during or as a consequence of use of a medicinal product in human clinical trials, will also be considered AEs.

An AE does not include:

- Medical or surgical procedures (*e.g.*, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected prior to study entry that do not worsen.
- Situations where an untoward medical occurrence has not occurred (*e.g.*, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (see Section 7.4).

7.2. Assessment of Adverse Events

AEs that (1) meet the criteria for a serious adverse event (SAE) (as defined in Section 7.3), (2) lead to permanent discontinuation of the study drug, emtricitabine, and/or (3) are associated with skin discoloration (hyperpigmentation) will be assessed by the Investigator and recorded on the appropriate CRF page, including the date of onset and resolution, severity, relationship to study drug or study procedures, emtricitabine, outcome and action taken with the study drug. No other AEs will be recorded.

Severity should be recorded and graded according to the GSI-modified DAIDS/NIAID Common Toxicity Grading Scale (see Appendices 3 and 4 to this protocol). The relationship to the study drug, emtricitabine, or study procedures should be assessed using the following definitions:

- **No**: Evidence exists that the AE has an etiology other than the study drug or study procedures (*e.g.*, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: A temporal relationship exists between the event onset and administration of the study drug or between the event and the study procedures. It cannot be readily explained by the subject's clinical state or concomitant therapies and, in the case of the study drug, appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon re-challenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to the study drug, then an alternative explanation should be provided.

7.3. Serious Adverse Events

A SAE is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at **immediate** risk of death);
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Other: medically significant events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

  Examples of such events are:

  — Intensive treatment in an emergency room or at home for allergic bronchospasm

  — Blood dyscrasias or convulsions that do not result in hospitalization

  — Development of drug dependency or drug abuse.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug.

- All deaths, regardless of cause or relationship, must be reported for subjects on study and for deaths occurring within 30 days of last study drug dose or within 30 days of last study evaluation, whichever is longer.

- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between serious and severe AEs. An AE that is assessed as grade 4 (potentially life-threatening) should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as grade 4.

7.4. Special Situations Reports

7.4.1. Definitions of Special Situations

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse,or overdose, and reports of adverse reactions associated with product complaints.

For this study, a pregnancy report is used to report pregnancies following maternal exposure to the product.

Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product while in the control of the HCP, patient or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a patient.

Misuse is defined as any use of a medicinal product in a way that the product is intentionally and inappropriately used not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol (as it applies to the dose for the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

7.4.2. Instructions for Reporting Special Situations

7.4.2.1. Instructions for Reporting Pregnancies

The Investigator should report all pregnancies to Gilead DSPH using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the adverse event term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in the Adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to Gilead Sciences.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the Pregnancy Outcome Report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Refer to Section 7.9 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

7.4.2.2. Reporting Other Special Situations

All other Special Situation reports must be reported on the Special Situations Report Form and forwarded to Gilead DSPH within 24 hours. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

All clinical sequelae in relation to these special situation reports that meet criteria for AE or SAE reporting will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

7.5. Serious Adverse Event Reporting Requirements

7.5.1. All Serious Adverse Events

GSI has requirements for expedited reporting of SAEs meeting specific requirements to worldwide regulatory authorities; therefore, GSI must be notified immediately regarding the occurrence of any SAE that occurs after the screening (initial) visit, including SAEs resulting from study procedures performed from screening onwards. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- Record the SAE on the AE CRF and complete the "Serious Adverse Event Report" form.
- Fax the SAE report to the attention of the Gilead Department of Safety and Public Health (DSPH) SAE Report Form within 24 hours of the Investigator's knowledge of the event. GDS contact information is provided below.
- For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

Gilead Sciences DSPH:	Telephone:	PPD
	Fax:	PPD
	Email:	safety_fc@gilead.com
GSI Medical Monitor:	Name:	Erin Quirk, M.D.
	Telephone:	PPD
	Fax:	PPD
	Mobile:	PPD
	Email:	PPD

- For fatal or life-threatening events, also e-mail or fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable. Transmission of such documents should occur with Personal Subject Details de-identified, without losing the traceability of a document to the Subject Identifiers.

- Gilead Sciences may request additional information from the Investigator to ensure the timely completion of accurate safety reports.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF.

Follow-up of AEs will continue through the last day on study (including the follow-up, off study drug period of the study), until the Investigator and/or GSI determine that the subject's condition is stable, or up to 30 days after the last dose of study drug, whichever is longer. GSI may request that certain AEs be followed until resolution.

7.5.2. Investigator Reporting Requirements for SAEs

A SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug, and is unexpected based upon the current Company Core Safety Information appended to the emtricitabine Investigator's Brochure. In this case, all Investigators will receive a formal notification describing the SAE.

The Investigator should notify the Independent Ethics Committee (IEC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

7.5.3. Post Study Reporting Requirements

All deaths, regardless of cause or relationship, must be reported for subjects on study and for all deaths occurring within 30 days of last study drug dose.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Clinical laboratory abnormalities (e.g., clinical chemistry, hematology or urinalysis) or other abnormal findings (e.g., electrocardiogram, X-rays or vital signs) performed as part of current standard of care should not be recorded as adverse events in the CRF unless serious and/or they lead to the discontinuation of study drug, emtricitabine. Wherever possible, the Investigator should attempt to establish a diagnosis of the event, based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. The results of routine clinical laboratory (hematology, clinical chemistry and urinalysis), immunological data (absolute and percent CD4+), pregnancy test results, and physical examination findings collected in the FTC-203 study will no longer be collected or recorded in the CRF, nor will the findings of any assessments done according to current standard of care practices during the rollover protocol be recorded in the CRF.

7.7. Toxicity Management

Clinical events that meet the criteria for an SAE and/or that lead to discontinuation of the study drug, emtricitabine, will be graded according to the GSI-modified DAIDS/NIAID Common Toxicity Grading Scale (see Appendices 3 and 4). The relationship to study drug or study procedures will be assessed using the definitions outlined in Section 7.2.

For any toxicity, Investigators are urged to identify the drug most likely to be the cause of the toxicity and change that drug or dosage, if possible. To manage specific toxicities associated with background antiretroviral medications, the Investigator should follow the current package insert, manufacturer's guidelines and/or Investigator's Brochure for the individual drugs. If a subject becomes intolerant to emtricitabine, the decision to interrupt, dose adjust and/or discontinue the medication must be promptly communicated to the GSI Medical Monitor. Brief (generally ≤ 14 days) interruptions in treatment are permitted, *e.g.*, to manage a newly emergent toxicity. Longer (> 14 days) interruptions are permitted only with the approval of the GSI Medical Monitor and will be decided on a case-by-case basis. The GSI Medical Monitor will be available for consultation on all toxicity-related issues (see Section 7.5.1 for contact information).

7.8. Major Toxicities of Emtricitabine

The most common side effects seen in subjects treated with emtricitabine in combination with other anti-HIV drugs are: allergic reaction, headache, dizziness, insomnia, abnormal dreams, diarrhea, nausea, vomiting, problems with digestion resulting in gastrointestinal discomfort after meals, abdominal pain, rash, changes in skin color on the palms and/or soles, pain, feeling tired or weak, increased triglycerides levels, adverse effects on the function of the liver (*e.g.*, elevated bilirubin), and pancreas, increased blood glucose, and low white blood cell count. Increases in creatine kinase, associated with muscle pain and weakness, have also been reported. Anemia has been reported in pediatric subjects treated with emtricitabine.

See the emtricitabine Investigator's Brochure for more detailed information.

7.8.1. Skin Discoloration

In the adult clinical trials, skin discoloration was reported more frequently in patients treated with emtricitabine, as compared to patients enrolled in control groups {7095}. The skin discoloration occurred as hyperpigmentation, most commonly on the palms and/or soles, and was always mild or moderate, generally asymptomatic and without association with any pathologic skin condition.

In the event that a subject should develop hyperpigmentation while participating in this rollover protocol, the hyperpigmentation should be documented in the CRF as an adverse event and a Hyperpigmentation Assessment CRF completed. In addition, the subject may be required to have one or more dermatological consultations and possibly other explorations, as

deemed necessary by the dermatologist. Any relevant medical consultation should be retained in the study files and appended to the subject's CRF.

7.9. Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with the study drugs during pregnancy have not been evaluated. If females are using hormonal agents for contraception, the safety and/or efficacy may be affected by possible drug-drug interaction. Subjects receiving hormonal contraceptives should consider additional methods of contraception as concentrations of ethinyl estradiol may decrease and progestin level may increase on coadministration with study drugs. If females utilize hormonal agents as one of their contraceptive methods, it is required that the same hormonal method be used for at least 3 months before study dosing.

For additional information, please refer to the Prescribing Information for Emtricitabine.

7.9.1. Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This includes pubertal females regardless of whether or not she has had a menses (premenarchal, Tanner Stage 3) and perimenopausal women who have had a spontaneous menses in the last 12 months.

- Women ≤ 54 years of age with amenorrhea of any duration will be considered to be of childbearing potential. Exceptions must be discussed with the Medical Monitor.

- Women > 54 years of age with cessation (for ≥12 months) of previously occurring menses due to ovarian failure will not be considered to be of childbearing potential.

7.9.2. Contraception Requirements

Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-recommended method(s) of contraception from 3 weeks prior to baseline, throughout the study period and for 30 days following the last dose of study medication. The investigator should counsel subjects on the protocol-recommended method(s) for avoiding pregnancy during the trial. These methods are recommended due to the low failure rate (i.e., less than 1% per year). See Table 7-1 for the protocol-recommended methods.

Female study subjects who are not heterosexually active must have periodic confirmation of continued abstinence from heterosexual intercourse as a lifestyle choice and regular pregnancy testing while taking study drugs. The investigator should counsel subjects on the protocol-recommended method(s) for avoiding pregnancy in case subject chooses to engage in heterosexual intercourse.

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and at Baseline (Day -1) prior to receiving the first dose of study drug. Lactating females must discontinue nursing before investigational medicinal product administration.

Table 7-1. Protocol-Recommended Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	**Barrier Methods (use both OR choose one and use with a hormone method)**
Intra-uterine devices (IUDs) • Copper T 380A IUD • LNg 20 IUD **Tubal sterilization**	**Estrogen and Progesterone** • Oral contraceptives • Transdermal Patch • Vaginal Ring **Progesterone** • Injection • Implant	• Diaphragm with spermicide OR Cervical cap with spermicide • Male condom (no lambskin condoms and without spermicide)
	Partner's vasectomy must be used along with a hormone or barrier method.	

Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom (except lambskin).

Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after micro-insertion. Prior to verification, Essure is not considered a reliable form of contraception and another contraception method described above should be used.

Other contraceptive methods may be acceptable after discussion with the Medical Monitor.

7.9.3. Additional Requirements for Male Subjects

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for 30 days after administration of the last dose of study drug.

Use of condoms (except for lambskin) should be encouraged for all participants because they have been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is HIV-infected.

7.9.4. Risks for Women of Childbearing Potential or During Pregnancy

The risks of treatment with the study drug, emtricitabine, during pregnancy have not been evaluated. Animal studies do not indicate direct or indirect harmful effects of emtricitabine with respect to pregnancy. Please refer to the latest version of the Investigator's Brochure for additional information. Barrier contraception should always be used in combination with other methods of contraception (*e.g.*, oral or other hormonal contraceptives) by females of child bearing potential who are less than 2 years post-menopausal while participating in the study and for 30 days following the last dose of study drug. Male subjects in the study who are sexually active must use barrier contraception for the same period of time with their female partners of childbearing potential or agree to abstain from heterosexual intercourse for the duration of their participation in the study.

The subject must be instructed to discontinue the study drug (and other medications, as applicable) and inform the Investigator **immediately** if she becomes pregnant during the study.

The Investigator should report all pregnancies to the GSI within 24 hours of becoming aware of the pregnancy. The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study center of the outcome of the pregnancy.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an SAE. A spontaneous abortion is always considered to be an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to GSI.

Additionally all pregnancies that occur during the study should be reported using the Pregnancy Report CRF page. Monitoring of the subject should continue until the conclusion of the pregnancy. The outcome should be reported to GSI using the Pregnancy Outcome (and Abnormal Pregnancy Outcome, if applicable) CRF page(s). If the end of the pregnancy occurs after the study has been complete, the outcome should be reported directly to GSI. Pregnancies that occur after the subject has discontinued study drugs do not require monitoring.

8. STATISTICAL CONSIDERATIONS

No statistical analysis are planned. Data listings will be generated for all data collected in the clinical database. Listings will include subject enrollment/disposition, demographics (from the FTC-203 clinical database), SAEs, AEs leading to permanent discontinuation of study drug, emtricitabine, AEs associated with skin discoloration (hyperpigmentation), and study drug dispensing/accountability. Tabular summaries will be prepared.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a US IND, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

9.1.2. Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the Investigator, to an independent ethics committee (IEC) and, where applicable, to the relevant regulatory and/or health authorities in each respective country. Approval from the IEC and, where applicable, the relevant regulatory/health authority(ies) must be obtained **before** starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the IEC met and granted the approval.

Any modifications made to the protocol after receipt of IEC approval must also be submitted to the IEC and, where applicable, the relevant regulatory/health authority(ies) for approval prior to implementation.

9.1.3. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The Investigator must utilize an IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

9.1.4. Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials and an identification code (*i.e.*, not names) should be recorded on any form submitted to the Sponsor

and IEC. The Investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The Investigator agrees that all information received from GSI, including but not limited to the Investigator's Brochure, this protocol, CRFs, the investigational new drug, and any other study information remain the sole and exclusive property of GSI during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from GSI. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (although not limited to) the following: (1) Investigator's study file, and (2) subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, CRF and query forms, IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not, limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, *etc*.

All clinical study documents must be retained by the Investigator until at least two years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region (*i.e.*, US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or an agreement with GSI. The Investigator must notify GSI Sciences prior to destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, GSI must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and GSI to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the

continued care of the subject, appropriate copies should be made for storage outside of the site.

9.1.6. Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the Investigator or Sub-investigator within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

9.1.7. Drug Accountability

The Investigator or designee (*i.e.*, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and subject dispensing records and returned or destroyed study product. Dispensing records will document quantities received from GSI and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with GSI requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according these procedures. If the site cannot meet GSI's requirements for disposal, arrangements will be made between the site and GSI or it's representative, for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

9.1.8. Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from GSI or its representatives, to IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by GSI. All protocol modifications must be submitted to the IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

After conclusion of the study and without prior written approval from GSI, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- the results of the study in their entirety have been publicly disclosed by or with the consent of GSI in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include GSI's confidential information (see Section 9.1.4).

The Investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation. The Investigator will comply with GSI's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of GSI may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority the Investigator agrees to notify the GSI Medical Monitor immediately. The Investigator agrees to provide to representatives of a regulatory agency or GSI access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.3. Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory/health authority(ies) and IECs. In terminating the study, GSI and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

7095 Mondou E, Hinkle J, Shaw A, Quinn J, Adda N, Rousseau F. Incidence of skin discoloration across phase 3 clinical trials of emtricitabine (FTC) in adults [poster 5916]. XV International AIDS Conference; 2004 July 11-16; Bangkok, Thailand.

7438 Saez-Llorens X, Violari A, Ndiweni D, Avila-Figueroa C, Wiznia A, Blum MR, et al. Once Daily Emtricitabine (FTC) in HIV-Infected Pediatric Patients with Other Antiretroviral Agents [Poster 872]. 10th Conference on Retroviruses and Opportunistic Infections; 2003 February 10-14; Boston, MA.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DR.
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT
A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine

GS-US-162-0112 Protocol Amendment: 24 July 2013

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

ERIN QUIRK

Erin Quirk, MD
Author

PPD

Signature

26- July -2013

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Emtricitabine (Emtriva®) Dose Tables

EMTRIVA® CAPSULE, 200 mg			
Body Weight Range (kg)	**Calculated Dose Range at 6 mg/kg (mg)**	**Actual Dose To Administer (mg)**	**Number of 200 mg Capsules To Administer**
< 32.9	N/A	NA	Use Solution
≥ 33	≥ 189.6	200	1

EMTRIVA® ORAL SOLUTION, 10 mg/mL					
Body Weight Range (kg)		**Calculated Dose Range at 6 mg/kg (mg)**		**Actual Dose To Administer (mg)**	**Volume of 10 mg/mL Solution to Administer (mL)**
Min.	**Max.**	**Min.**	**Max.**		
2.5	3.3	15.0	19.8	20	2.0
3.4	4.1	20.4	24.6	25	2.5
4.2	4.9	25.2	29.4	30	3.0
5.0	5.7	30.0	34.2	35	3.5
5.8	6.5	34.8	39.0	40	4.0
6.6	7.4	39.6	44.4	45	4.5
7.5	8.2	45.0	49.2	50	5.0
8.3	9.1	49.8	54.6	55	5.5
9.2	10.0	55.2	60.0	60	6.0
10.1	10.8	60.6	64.8	65	6.5
10.9	11.6	65.4	69.6	70	7.0
11.7	12.5	70.2	75.0	75	7.5
12.6	13.3	75.6	79.8	80	8.0
13.4	14.1	80.4	84.6	85	8.5
14.2	15.0	85.2	90.0	90	9.0
15.1	15.8	90.6	94.8	95	9.5
15.9	16.6	95.4	99.6	100	10.0
16.7	18.3	100.2	109.8	110	11.0
18.4	20.0	110.4	120.0	120	12.0
20.1	21.6	120.6	129.6	130	13.0
21.7	23.3	130.2	139.8	140	14.0
23.4	25.0	140.4	150.0	150	15.0

EMTRIVA® ORAL SOLUTION, 10 mg/mL					
Body Weight Range (kg)		**Calculated Dose Range at 6 mg/kg (mg)**		**Actual Dose To Administer (mg)**	**Volume of 10 mg/mL Solution to Administer (mL)**
Min.	**Max.**	**Min.**	**Max.**		
25.1	26.6	150.6	159.6	160	16.0
26.7	28.3	160.2	169.8	170	17.0
28.4	30.0	170.4	180.0	180	18.0
30.1	31.5	180.6	189.0	190	19.0
31.6	33.3	189.6	199.8	200	20.0*
33.4	35.0	200.4	210.0	210	21.0*
35.1	36.6	210.6	219.6	220	22.0*
36.7	38.3	220.2	229.8	230	23.0*
≥ 38.4		≥ 230.4		240	24.0*

For subjects able to swallow solid medication, use the capsule formulation.

Appendix 3. Study Procedures Table

Assessment	FTC-203	GS-US-162-0112[1]		
	End-of-Study[2]	Baseline Visit[3]	+ each 12 weeks[4]	Subject Discontinuation
Informed Consent		x		
Review of Incl./Excl. Criteria		x		
Physical Examination	X			
Height/Weight/Vital Signs	X	x[5]	x[5]	x[5]
Hematology	X			
Chemistry	X			
Urinalysis	X			
Pregnancy Test[6]	X			
CD4+ Cell Count	X			
Plasma HIV-1 RNA Levels	X	X	X	X
Plasma for Storage (5 mL)	X			
Record Adverse Events	X	x[7]	x[7]	x[7]
Record HIV-1 Related Events	X			
Study Drug Accountability	X	x	x	x
Dispense Study Drug[8]		x	x	
Concomitant Medications	X			

1 Only for qualifying subjects, i.e., subjects who meet the virologic criteria for continuation of emtricitabine at the End-of-Study Visit for FTC-203 (see Section 6.2.2).

2 These assessments will be performed on all subjects who discontinue the FTC-203 study, regardless of reason, including those subjects who complete the FTC-203 study and who elect not to participate in the rollover protocol.

3 If there is a reasonable expectation that the subject will continue to meet the virologic criteria for continuation of emtricitabine, based on the results of HIV-1 RNA viral load testing performed during the FTC-203 study, then the End-of-Study Visit for FTC-203 and the Baseline Visit of the GS-US-162-0112 rollover protocol may be completed at the same clinic visit.

4 The Investigator may choose to have the subject return to the clinic on a more frequent basis, e.g., as part of their standard of care, and/or to resupply the study drug(s) (and other medications) but these visits will be outside of the protocol-defined visit schedule.

5 Height (or length) and body weight only, if the subject has not maintained the same height for three consecutive protocol visits (36 weeks), or if the height and weight are necessary to determine study drug dosage.

6 If the pregnancy test is positive, discontinue emtricitabine and contact GSI. A positive urine β-HCG test should be confirmed with a serum β-HCG test, per the FTC-203 protocol.

7 Adverse events will only be recorded in the CRF if the event (s) is (1) serious, (2) results in the permanent discontinuation of study drug, emtricitabine, and/or (3) is associated with skin discoloration (hyperpigmentation).

8 Subjects will receive emtricitabine, in combination with other antiretroviral medications, at 6 mg/kg once daily (QD), up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD using the oral solution formulation, each administered orally, for as long as the subject continues to demonstrate virologic success. Although assessments are scheduled at 12-week intervals, no more than a 60-day supply of emtricitabine oral solution may be dispensed to subjects who do not have means to adequately refrigerate the drug at home, thereby necessitating more frequent visits by the subject to the clinic to resupply the study drug. Drug accountability information will be recorded at those visits.

Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	1000 to 1300/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/microL	200 to < 300/mm^3 200 to < 300/microL	100 to < 200/mm^3 100 to < 200/microL	< 100/mm^3 < 100/microL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100.0 to < 125.0 GI/L	50,000 to < 100,000/mm^3 50.0 to < 100.0 GI/L	25,000 to < 50,000/mm^3 25.0 to < 50.0 GI/L	< 25,000/mm^3 < 25.0 GI/L
WBCs	2000/mm^3 to 2500/mm^3	1,500 to < 2,000/mm^3	1000 to < 1,500/mm^3	< 1000/mm^3
	2.0 GI/L to 2.5 GI/L	1.5 to < 2.0 GI/L	1.0 to < 1.5 GI/L	< 1.0 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypofibrinogenemia	100 to < LLN mg/dL	75 to < 100 mg/dL	50 to < 75 mg/dL	< 50 mg/dL
	1.00 to < LLN g/L	0.75 to < 1.00 g/L	0.50 to < 0.75 g/L	< 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL	> 600 mg/dL	—	—
	> ULN to 6.0 g/L	> 6.0 g/L		
Fibrin Split Product	20 to 40 microg/mL	> 40 to 50 microg/mL	> 50 to 60 microg/mL	> 60 microg/mL
	20 to 40 mg/L	> 40 to 50 mg/L	> 50 to 60 mg/L	> 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
Activated Partial Thromboplastin (APPT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 mEq/L to < LLN	125 to < 130 mEq/L	121 to < 125 mEq/L	< 121 mEq/L
	130 mmol/L to < LLN	125 to < 130 mmol/L	121 to < 125 mmol/L	< 121 mmol/L
Hypernatremia	> ULN to 150 mEq/L	> 150 to 154 mEq/L	> 154 to 159 mEq/L	> 159 mEq/L
	> ULN to 150 mmol/L	> 150 to 154 mmol/L	> 154 to 159 mmol/L	> 159 mmol/L
Hypokalemia	3.0 mEq/L to < LLN	2.5 to < 3.0 mEq/L	2.0 to < 2.5 mEq/L	< 2.0 mEq/
	3.0 mmol/L to < LLN	2.5 to < 3.0 mmol/L	2.0 to < 2.5 mmol/L	< 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L	> 6.0 to 6.5 mEq/L	> 6.5 to 7.0 mEq/L	> 7.0 mEq/L
	5.6 to 6.0 mmol/L	> 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mmol/L	> 7.0 mmol/L
Hypoglycemia **Adult and Pediatric** **≥ 1 Month**	55 to 64 mg/dL	40 to < 55 mg/dL	30 to < 40 mg/dL	< 30 mg/dL
	3.1 to 3.5 mmol/L	2.2 to < 3.1 mmol/L	1.7 to < 2.2 mmol/L	< 1.7 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting and No Prior Diabetes	> ULN to 160 mg/dL	> 160 to 250 mg/dL	> 250 to 500 mg/dL	> 500 mg/dL
	> ULN to 8.9 mmol/L	> 8.9 to 13.9 mmol/L	> 13.9 to 27.7 mmol/L	> 27.7 mmol/L
Hypocalcemia (corrected for albumin) **Adult and Pediatric** **≥ 7 Days**	7.8 mg/dL to < LLN	7.0 to < 7.8 mg/dL	6.1 to < 7.0 mg/dL	< 6.1 mg/dL

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	1.94 mmol/L to < LLN	1.74 to < 1.94 mmol/L	1.51 to < 1.74 mmol/L	< 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin) **Adult and Pediatric ≥ 7 Days**	> ULN to 11.5 mg/dL	> 11.5 to 12.5 mg/dL	> 12.5 to 13.5 mg/dL	> 13.5 mg/dL
	> ULN to 2.88 mmol/L	> 2.88 to 3.13 mmol/L	> 3.13 to 3.38 mmol/L	> 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL	> 6.0 to 6.5 mg/dL	> 6.5 to 7.0 mg/dL	> 7.0 mg/dL
	> ULN to 1.50 mmol/L	> 1.50 to 1.63 mmol/L	> 1.63 to 1.75 mmol/L	> 1.75 mmol/L
Hypomagnesemia	1.45 mg/dL to < LLN	1.09 to < 1.45 mg/dL	0.72 to < 1.09 mg/dL	< 0.72 mg/dL
	0.60 mmol/L to < LLN	0.45 to < 0.60 mmol/L	0.30 to < 0.45 mmol/L	< 0.30 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 mg/dL to < LLN	1.5 to < 2.0 mg/dL	1.0 to < 1.5 mg/dL	< 1.0 mg/dL
	0.63 mmol/L to < LLN	0.47 to < 0.63 mmol/L	0.31 to < 0.47 mmol/L	< 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to 3.5 mg/dL 0.96 to 1.14 mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 micromol/L	> 25.0 to 30.0 mg/dL > 428 to 513 micromol/L	> 30.0 mg/dL > 513 micromol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 micromol/L	> 25.0 mg/dL > 428 micromol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	> ULN to 10.0 mg/dL	> 10.0 to 12.0 mg/dL	> 12.0 to 15.0 mg/dL	> 15.0 mg/dL
	> ULN to 597 micromol/L	> 597 to 716 micromol/L	> 716 to 895 micromol/L	> 895 micromol/L
Hypouricemia	1.5 mg/dL to < LLN	1.0 to < 1.5 mg/dL	0.5 to < 1.0 mg/dL	< 0.5 mg/dL
	90 micromol/L to < LLN	60 to < 90 micromol/L	30 to < 60 micromol/L	< 30 micromol/L
Creatinine	> 1.5 to 2.0 mg/dL	> 2.0 to 3.0 mg/dL	> 3.0 to 6.0 mg/dL	> 6.0 mg/dL

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	> 137 to 181 micromol/L	> 181 to 269 micromol/L	> 269 to 535 micromol/L	> 535 micromol/L
Bicarbonate	16.0 mEq/L to < LLN	11.0 to < 16.0 mEq/L	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
	16.0 mmol/L to < LLN	11.0 to < 16.0 mmol/L	8.0 to < 11.0 mmol/L	< 8.0 mmol/L
Triglycerides (Fasting)	—	500 to 750 mg/dL	> 750 to 1200 mg/dL	> 1200 mg/dL
		5.64–8.47 mmol/L	> 8.47–13.55 mmol/L	> 13.55 mmol/L
Hypercholesterolemia (Fasting)	200 to 239 mg/dL	> 239 to 300 mg/dL	> 300 mg/dL	—
	5.16 to 6.19 mmol/L	> 6.19 to 7.77 mmol/L	> 7.77 mmol/L	
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN
Lactate	ULN to < 2.0 × ULN without acidosis	≥ 2.0 × ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN	2.0 to < 3.0 g/dL	< 2.0 g/dL	—
	30 g/L to < LLN	20 to < 30 g/L	< 20 g/L	

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3+	NA
Hematuria (Quantitative)	6–10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	> 999 to 1999 mg/24 h	> 1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	> 499 to 799 mg/m^2/24 h	> 799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2+	3+	4+

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	> 140–159 mmHg systolic OR > 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization (other than ER visit) indicated
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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 nonurgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR Interval	PR interval 0.21 to 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
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 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 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 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)

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	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% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for 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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
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/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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) See also Proctitis, Dysphagia-Odynophagia	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)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (e.g., sepsis, circulatory failure, hemorrhage)
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)

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	Life-threatening consequences (e.g., hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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/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 ADD)	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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 ER visit) OR Headache with significant impairment of alertness or other neurologic function

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (pre-existing) 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 breakthrough seizures while on stable meds 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 that 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

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-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
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

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, 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 ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 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]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^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)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (e.g., back of neck, breasts, abdomen)	Detectable by study participant or 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 meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
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 caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual 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

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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)

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

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