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. 4 University Place, 4611 University Drive Durham, North Carolina 27707, USA Telephone: 001-919-493-5980 Fax: 001-919-493-5925
IND No.:	53,971
EudraCT No.:	Not applicable
Protocol ID:	GS-US-162-0112
Gilead Medical Monitor:	Name: Nathalie Adda, M.D. Senior Clinical Research Physician, Clinical Research Telephone: PPD Cellphone: PPD Fax: PPD
CRO Medical Monitor:	Not applicable
Protocol Version/ Date:	Final: 24 January, 2005 Original

CONFIDENTIALITY STATEMENT

GILEAD SCIENCES, INC.

4 UNIVERSITY PLACE, 4611 UNIVERSITY DRIVE
DURHAM, NC 27707, USA

STUDY ACKNOWLEDGEMENT

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

Final, 24 January 2005

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

Nathalie Adda

PPD

Nathalie Adda, M.D.
Medical Monitor / Sr. Clinical Research Physician

Signature

02-02-05

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.

_____ _____

Investigator Name (Print) Investigator Signature

_____ _____

Date Site Number

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
4 University Place, 4611 University Drive, Durham, NC 27707, USA

Title of Study:	A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine
IND Number:	53,971
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.

PROTOCOL SYNOPSIS (CONTINUED)

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.

PROTOCOL SYNOPSIS (CONTINUED)

Study Procedures/ Frequency (cont.):	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. If genotypic analysis is 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, this will be performed by the Clinical Virology and Diagnostics group, Gilead Sciences, Inc. (Durham).
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.

PROTOCOL SYNOPSIS (CONTINUED)

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 7.7.1). 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. Acceptable methods of contraception include an intra-uterine device or barrier contraceptives (*i.e.*, cap/diaphragm, male condom, female condom, *etc.*) with a spermicide. Because the effects of emtricitabine on hormonal contraceptives have not been characterized, oral and depot contraceptives (*i.e.*, implant or injectable) must be used in conjunction with an acceptable barrier contraceptive. See Section 7.8 for more information on contraception and pregnancy.

- 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 Eighth Edition of the Emtricitabine (FTC) Brochure, dated 30 June 2003.)

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 ≤ 60 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 Eighth Edition of the Emtricitabine (FTC) Brochure, dated 30 June 2003.)

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 by the Clinical Virology and Diagnostics group, GSI (Durham). 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 Durham 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, and 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. If genotypic analysis is 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, this will be performed by the Clinical Virology and Diagnostics group, Gilead Sciences, Inc. (Durham).

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 not 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.

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 of either the study drug, emtricitabine, or a concomitant medication without any signs or symptoms unless the subject is hospitalized for observation.

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. Serious Adverse Event Reporting Requirements

7.4.1. 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 GSI Global Drug Safety Department (GDS) 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.

GSI Global Drug Safety:	Name:	PPD Manager, GDS
	Telephone:	PPD (Working Days)
	Fax:	PPD
	Email:	PPD
GSI Medical Monitor:	Name:	Nathalie Adda, M.D. Sr. Clinical Research Physician, Clinical Research
	Telephone:	PPD (Working Days) / PPD (Medical Emergencies)
	Cellphone:	PPD
	Fax:	PPD
	Email:	PPD

GSI 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.

7.4.2. 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.

7.4.3. 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.

7.5. 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.

7.6. 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 7.4.1 for contact information).

7.7. 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.

7.7.1. 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.

7.8. 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 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.

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]. XV International AIDS Conference; 2004 July 11-16; Bangkok, Thailand. Poster Number 5916.

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. 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
< 31.5	N/A	NA	Use Solution
≥ 31.6	≥ 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
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 2. 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			
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.
6. If the pregnancy test is positive, 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 3. Toxicity Tables for Grading the Severity of Adverse Events in Pediatric Subjects Aged ≥ 3 Months to < 13 Years Old

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HEMATOLOGY				
Hemoglobin (g/dL) ages > 3 mo. to < 2 yr.	9.0 – 9.9	7.0 – 8.9	< 7.0	Cardiac failure secondary to anemia
Hemoglobin (g/dL) ages ≥ 2 yr. to < 13 yr.	10 – 10.9	7.0 – 9.9	< 7.0	Cardiac failure secondary to anemia
Absolute Neutrophil Count (cells/mm^3)	750 – 1200	400 – 749	250 – 399	< 250
Platelet Count (/mm^3)	—	50,000 – 75,000	25,000 – 49,999	<25,000 or bleeding
PT (sec)	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 3.00 × ULN	>3.00 × ULN
PTT (sec)	1.1 – 1.66 × ULN	1.67 – 2.33 × ULN	2.34 – 3.00 × ULN	>3.00 × ULN
GASTROINTESTINAL				
Bilirubin (mg/dL)	1.1 – 1.9 × ULN	2.0 – 2.9 × ULN	3.0 – 7.5 × ULN	> 7.5 × ULN
Cholesterol	171 – 499 mg/mL	500 – 749 mg/mL	≥ 750 mg/mL	See Grade 3
Triglyceride	136 – 749 mg/dL	750 – 1199 mg/dL	≥ 1200 mg/dL	See Grade 3
AST (SGOT) (U/L)	1.1 – 4.9 × ULN	5.0 – 9.9 × ULN	10.0 – 15.0 × ULN	> 15.0 × ULN
ALT (SGPT) (U/L)	1.1 – 4.9 × ULN	5.0 – 9.9 × ULN	10.0 – 15.0 × ULN	> 15.0 × ULN
GGT (U/L)	1.1 – 4.9 × ULN	5.0 – 9.9 × ULN	10.0 – 15.0 × ULN	> 15.0 × ULN
Pancreatic Amylase (U/hour)	1.1 – 1.4 × ULN	1.5 – 1.9 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN
Total Amylase + Lipase*	1.1 – 1.4 × ULN	1.5 – 2.4 × ULN	2.5 – 5.0 × ULN	> 5.0 × ULN
Uric Acid (mg/dL)	7.5 – 9.9	10.0 – 12.4	12.5 – 15.0	> 15.0 or gout
CPK (U/L)	See Neuromuscular Toxicity			
Abdominal Pain	Mild	Moderate – no Rx needed	Moderate – Rx needed	Severe – hospital and Rx needed
Diarrhea	Soft stools	Liquid stools	Liquid stools & mild dehydration/bloody stools	Dehydration requiring IV therapy or hypotensive shock
Constipation	Mild	Moderate	Severe	Distention & vomiting
Nausea	Mild	Moderate – decreased po intake	Severe – little po intake	Unable to ingest food or fluid for > 24 hours
Vomiting	< 1 episode/day	1-3 episodes/day or duration > 3 days	> 3 episodes/day or duration > 7 days	Intractable vomiting

* Both amylase and lipase must be elevated to the same grade or higher (*i.e.*, if total amylase is Grade 4, but lipase is only Grade 1, the Toxicity Grade is 1. In pediatric HIV patients, the most common source of serum amylase is the salivary glands. Salivary amylase elevations are generally not clinically significant. When amylase is released from damaged pancreatic cells, it can be a marker of pancreatitis. In most cases of clinical pancreatitis, lipase will also be elevated. However, lipase is also a non-specific marker. Combined elevation of amylase and lipase (each > 6 x ULN) often indicates pancreatic disease and requires evaluation. However, in the absence of pancreatic disease, drug can be resumed even at Grade 3 and 4 toxicities.

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
RENAL & ELECTROLYTES				
Creatinine (mg/dL) > 3 mo. to < 2 yr.	0.6 – 0.8	0.9 – 1.1	1.2 – 1.5	> 1.5
Creatinine (mg/dL) ≥ 2 yr. to < 13 yr.	0.7 – 1.0	1.1 – 1.6	1.7 – 2.0	> 2.0
Creatinine Clearance (CL_{cr})	60 – 75 mL/min/1.73 m^2	50 – 59 mL/min/1.73 m^2	35 – 49 mL/min/1.73 m^2	< 35 mL/min/1.73 m^2
ELECTROLYTES				
High Sodium (mEq/L)	—	145 – 149	150 – 155	> 155 or mental status changes
Low Sodium (mEq/L)	—	130 – 135	129 – 124	< 124 or mental status changes
High Potassium (mEq/L)	5.0 – 5.9	6.0 – 6.4	6.5 – 7.0	> 7.0 or cardiac arrhythmias
Low Potassium (mEq/L)	3.0 – 3.5	2.5 – 2.9	2.0 – 2.4	< 2.0
High Calcium (mg/dL)	10.5 – 11.2	11.3 – 11.9	12.0 – 12.9	≥ 13.0
Low Calcium (mg/dL)	7.8 – 8.4	7.0 – 7.7	6.0 – 6.9	< 6.0
Low Magnesium (mEq/L)	1.2 – 1.4	0.9 – 1.1	0.6 – 0.8	< 0.6 or cardiac arrhythmias
Hypoglycemia (mg/dL)	55 – 65	40 – 54	30 – 39	< 30 or mental status changes
Hyperglycemia (mg/dL)	116 – 189	160 – 249	250 – 400	> 400 or ketoacidosis
Proteinuria	Trace-1+ or < 150 mg/day	2+ or ≥ 150 – 499 mg/day	3+ or 500 – 1000 mg/day	4+ or nephrotic syndrome or > 1000 mg/day
Hematuria	Microscopic (< 25 cells/hpf)	Microscopic (≥ 25 cells/hpf)	Gross	Obstruction or transfusion requirement
Comments: Calcium values are corrected for albumin concentration. CL_{Cr} values do not apply to infants < 2 mo. old.				
MISCELLANEOUS				
Allergy	Pruritis without rash	Pruritic rash	Mild urticaria	Severe urticaria anaphylaxis, angioedema
Drug Fever (Rectal)	—	38.5 – 40°C	> 40°C	Sustained fever: > 40°C, > 5 days
Cutaneous	—	Diffuse maculopapular rash, dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Stevens-Johnson or erythema multiforme, moist desquamation
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: requires IV fluids
Seizures	None	1 uncomplicated seizure with or without temperature elevation	1 seizure/mo. for ≥2 consecutive mo. or 3 seizures	1 seizure/mo.; no temperature elevation; no decrease in

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
			over 6 mo.; no temperature elevation	seizure frequency despite dose reduction
Seizures are a ubiquitous symptom of numerous systemic or CNS disturbances; alternative explanations should be vigorously sought and eliminated. Status epilepticus represents a severe end of the seizure spectrum, but should be considered as a single seizure event. The need for chronic or acute anticonvulsant medication should be made on a clinical basis. Seizures as a manifestation of drug toxicity are usually primarily generalized. Focal (partial onset) seizures are suggestive of focal central nervous system pathology and should be appropriately investigated, although they may be a manifestation of drug toxicity. Beware of focal seizures, which secondarily generalize; these should be approached diagnostically as partial onset seizures. Children with underlying epileptic conditions who experience persistent breakthrough Seizures despite maximal anticonvulsant therapy coincident with beginning the trial medication should be considered Grade 4.				
Headache	≤ 1/mo. ≤ 2 hr duration mild	> 1/mo. >2 hr duration moderate to severe responds to non-narcotic analgesia or prophylaxis	> 2/mo. > 2 hr duration moderate to severe responds to narcotic analgesia, or does not respond to prophylaxis	> 4/mo. > 2 hr duration moderate to severe non-responsive to narcotic analgesia; or persistently recurrent despite prophylaxis no decrease in frequency or severity despite dose reduction
Headache is a non-specific symptom, but may be a symptom of CNS/intracranial pathology. Appropriate diagnostic measures should be pursued. Duration refers to the waxing and peak phases, not to the resolution/waning phases of the headache. Mild refers to a grade of headache pain that does not affect function or activity. Moderate to severe refers to a grade of headache, which affects function or activity.				
Mental Status And Behavior	Changes which do not affect function	Changes requiring pharmacologic or other therapy; or mild lethargy, sedation or somnolence which resolves with rest	Changes not improved by drugs or other therapies; or onset of confusion, memory impairment, lethargy, sedation, or somnolence which does not respond to rest	Onset of delirium, obtundation, coma, or psychosis, or Grade 3 toxicity which does not respond to dose reduction
Behavior refers to the development of attention deficits with or without hyperactivity, depression, mania, agitation, sleep disorders, phobias, obsessive-compulsive behaviors, or anxiety. Mental status refers to the level of consciousness, memory function, language and analytical operations, and non-dominant hemisphere functioning. Alternative explanations should be sought.				
Balance & Posture	None	None	Ataxia, dizziness, vertigo, tremor, impaired postural balance	Onset of movement disorder: or Grade 3 toxicity which does not respond to dosage adjustment
"Ataxia" can be mistakenly diagnosed in the face of central weakness or peripheral neuropathy, which should not be considered a drug toxicity of this category. Movement disorders refer to tardive or other dyskinesias, dystonias, chorea, or ballismus. Alternative explanations should be sought.				

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Visual	None	Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	≥ 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 Sx lasting 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis, or Grade 3 Sx which persist after dose reduction
Many of the symptoms in this category can be the result of CNS pathology, or alternatively can be an external (*i.e.*, non-CNS) neuro-opthalmologic disorder. Appropriate diagnostic investigations should be pursued.				
Myelopathy	None	None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction
HIV can cause spinal cord syndromes rarely in children. Other infectious agents can cause myelopathies as well. Alternative explanations should be sought.				
PERIPHERAL NERVOUS SYSTEM				
Neuropathy/Lower Motor Neuronopathy	None	Mild transient paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory distress from chest wall weakness. Grade 3 symptoms which do not resolve with dose reduction
Infectious agents other than HIV can precipitate a neuropathy and should be considered, especially CMV. Neuropathies that do not resolve after dose reduction or discontinuation should be pursued for alternative infectious or non-infectious etiologies, since drug-related neuropathies will usually resolve after dose reduction or drug discontinuation. It should be borne in mind that many patients will worsen for up to one month after drug discontinuation prior to improvement ("coasting"). Abnormalities should be confirmed by nerve conduction studies (NCS) +/- electromyographic studies (EMG).				
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x N) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN; Consider confirmatory EMG and/or muscle bx	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms (confirm with EMG); or Grade 3 symptoms which do not resolve on dose

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
				adjustment; confirm with muscle bx
HIV can produce a myopathy, and should be differentiated. Drug-induced myopathy can be accompanied by normal CPK levels. On occasion, neuropathic or central weakness can mimic myopathic weakness.				
OTHER				
Clinical symptoms not otherwise specified in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values not other-wise specified in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity. Requires immediate evaluation, treatment, and usually hospitalization. Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than study drug.

Appendix 4. Toxicity Tables for Grading the Severity of Adverse Events in Pediatric Subjects Aged ≥ 13 Years Old

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HEMATOLOGY				
Hemoglobin	8.0 - 9.4 g/dL	7.0 - 7.9 g/dL	6.5 - 6.9 g/dL	< 6.5 g/dL
Absolute white blood cell (WBC) Count	2001 - 3000/mm^3	1501 - 2000/mm^3	1001 – 1500/mm^3	≤ 1000/mm^3
Absolute Neutrophil Count	1000 - 1500/mm^3	750 - 999/mm^3	500 – 749/mm^3	< 500/mm^3
Platelets	75,000 - 99,000/mm^3	50,000 - 74,999/mm^3	20,000 - 49,999/mm^3	< 20,000/mm^3
Prothrombin Time (PT)	> 1.0 - 1.25 x ULN	> 1.25 - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 x ULN
Partial Thromboplastin Time (PTT)	> 1.0 - 1.66 x ULN	> 1.66 - 2.33 x ULN	> 2.33 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 - 10.0%	10.1 - 15.0%	15.1 - 20.0%	> 20%
CHEMISTRIES				
Sodium				
Hyponatremia	130 – 135 mEq/L	123 – 129 mEq/L	116 – 122 mEq/L	< 116 mEq/L
Hypernatremia	146 – 150 mEq/L	151 – 157 mEq/L	158 - 165 mEq/L	> 165 mEq/L
Potassium				
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 – 6.5 mEq/L	6.6 - 7.0 mEq/L	> 7.0 mEq/L
Hypokalemia	3.0 - 3.4 mEq/L	2.5 – 2.9 mEq/L	2.0 - 2.4 mEq/L	< 2.0 mEq/L
Phosphate				
Hypophosphatemia	2.0 - 2.4 mg/L	1.5 - 1.9 mg/L	1.0 - 1.4 mg/L	< 1.0 mg/L
Calcium - (corrected for albumin)				
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.1 - 6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL
Magnesium				
Hypomagnesemia	1.2 - 1.4 mEq/L	0.9 - 1.1 mEq/L	0.6 - 0.8 mEq/L	< 0.6 mEq/L
Bilirubin (total)				
Hyperbilirubinemia	> 1.0 - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 x ULN
Glucose				
Hypoglycemia	55 - 64 mg/dL	40 - 54 mg/dL	30 – 39 mg/dL	< 30 mg/dL
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161 - 250 mg/dL	251 – 750 mg/dL	> 750 mg/dL
Cholesterol	171 – 499 mg/mL	500 – 749 mg/mL	≥ 750 mg/mL	See Grade 3
Triglyceride	136 – 749 mg/dL	750 – 1199 mg/dL	≥ 1200 mg/dL	See Grade 3
Creatinine	> 1.0 - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Uric Acid				

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Hyperuricemia	7.5 - 10.0 mg/dL	10.1 - 12.0 mg/dL	12.1 - 15.0 mg/dL	> 15.0 mg/dL
Liver Transaminases (LFTs)				
AST (SGOT)	1.25 - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Gamma glutamyl transferase (GGT)	1.25 - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Alkaline Phosphatase	1.25 - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Creatine Phosphokinase (CPK) (unrelated to exercise)	> 1.0 - 2.0 x ULN	> 2.0 - 4.0 x ULN	> 4.0 - 6.0 x ULN	> 6.0 x ULN
Pancreatic Enzymes				
Amylase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 x 5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 x 5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 x 5.0 x ULN	> 5.0 x ULN
Albumin (total)	___	___	___	< 0.3 g/dL
URINALYSIS				
Proteinuria				
Spot urine	1+	2-3+	4+	Nephrotic syndrome
24 hour urine	200 mg - 1 g loss/day OR ≤ 0.3% OR ≤ 3 g/L	> 1 - 2 g loss/day OR > 0.3 - 1.0% OR > 3 - 10 g/L	> 2 - 3.5 g loss/day OR > 1.0% OR > 10 g/L	Nephrotic syndrome OR > 3.5 g loss/day
Gross Hematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive OR transfusion req
CARDIOVASCULAR				
Cardiac Arrhythmia	___	Asymptomatic; transient dysrhythmia, no Rx req	Recurrent/persistent dysrhythmia; symptomatic Rx req	Unstable dysrhythmia, hospitalization and Rx req
Hypertension	Transient, increase > 20 mm/Hg; no Rx	Recurrent; chronic increase > 20 mm/Hg, Rx req	Acute Rx req; outpatient hospitalization possible	Hospitalization req
Hypotension	Transient orthostatic hypotension, no Rx	Symptoms correctable with oral fluid Rx	IV fluid req, no hospitalization req	Hospitalization req
Pericarditis	Minimal effusion	Mild/mod asymptomatic effusion, no Rx	Symptomatic effusion, pain, EKG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, blood loss	___	Mildly symptomatic, no Rx required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
GASTROINTESTINAL				
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalization req
Vomiting	Mild OR transient; 2-3 episodes per day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥1 week	Severe vomiting of all food/fluids in 24 hours OR orthostatic hypotension OR IV Rx req	Hypotensive shock OR hospitalization req for IV Rx req
Diarrhea	Mild OR transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day OR diarrhea lasting ≥1 week	Bloody diarrhea; OR orthostatic hypotension OR > 7 loose stools/day OR IV Rx required	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting
Abdominal Pain	Mild discomfort; no limits on activity	Mild-moderate discomfort; no Rx req	Moderate pain; Rx req	Severe pain; hospitalization req
RESPIRATORY				
Cough (for aerosol studies)	Transient; no Rx	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic Rx req	___
Bronchospasm Acute	Transient; no Rx; FEV1 < 80% - 70% (or peak flow)	Rx req; normalizes with bronchodilator; FEV1 50% - < 70% (or peak flow)	No normalization with bronchodilator; FEV1 25% - < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O_2 therapy
NEUROLOGIC				
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with activities of daily living (ADL)	Unable to stand
Neuro-psych/mood	___	___	Severe mood changes requiring medical intervention	Acute psychosis req hospitalization
Paresthesia (burning tingling, *etc.*)	Bilateral and continuous mild discomfort; no Rx req	Bilateral and continuous mod discomfort (persisting > 3 days); non-narcotic analgesia req; no loss of deep tendon reflexes (DTRs); no worsening	Bilateral and continuous severe discomfort; (persisting for > 3 days) refractory to non-narcotic analgesia or requiring amitriptyline or	Incapacitating and not responsive to narcotic analgesia

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
		from a prior Grade 2 peripheral neuropathy followed for at least one week OR mild discomfort (persisting > 3 days) accompanied by loss of DTRs previously present.	clonazepam. OR Bilateral and continuous moderate discomfort (persisting for > 3 days) that has significantly worsened over a one week period. OR Bilateral and continuous (persisting for > 3 days) moderate discomfort that is accompanied by the loss of a previously present DTR.	
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness *e.g.*, in hands interfering with ADL and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheel chair because of muscle weakness
Neuro-sensory	Mild impairment (dec. sensation, *e.g.*, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment (mod dec. sensation, *e.g.*, vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (dec. or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (*i.e.*, upper and lower extremities)	Sensory loss involves limbs and trunks.
Myositis	Minimal findings	Positive electromyogram (EMG) or muscle biopsy and mild or moderate myalgias for > 4 weeks which may require non-steroidal anti-inflammatory agents; or difficulty climbing stairs or rising from a sitting position – can walk without assistance	Positive EMG or muscle biopsy and either moderate to severe myalgias for > 4 weeks requiring non-steroidal anti-inflammatory agents; or needs some assistance with walking or general activities	Positive EMG or muscle biopsy and either severe muscle pain not related to exercise, requiring narcotics; or muscle weakness with inability to walk requiring assistance; or acute rhabodmyolysis with muscle necrosis and edema, moderate to severe muscle weakness with inability to walk without

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
				assistance; or acute rhabodomyolysis with electrolyte imbalance or renal failure.
MISCELLANEOUS				
Fever (oral > 12 hours)	37.7 - 38.5°C OR 100.0 - 101.5°F	38.6 - 39.5°C OR 101.6 - 102.9°F	39.6 - 40.5°C OR 103 - 105°F	> 40.5°C OR > 105°F
Headache	Mild; no Rx req	Mod; or non-narcotic analgesia Rx	Severe; OR responds to initial narcotic Rx	Intractable; OR requiring repeated narcotic Rx
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria, angioedema	Anaphylaxis
Cutaneous/Rash/Dermatitis	Erythema	Diffuse maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme or necrosis requiring surgery
Local Reaction (2° parenteral Rx - not vaccination or skin test)	Erythema	Induration ≤ 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity reduced < 25%	Normal activity reduced 25 to 50%	Normal activity reduced > 50%; cannot work	Unable to care for self
Dizziness	Mild vertigo; no limits on activity	Moderate vertigo; limits activity	Moderate to severe vertigo; Rx required	Hospitalization required
Chills	Mild-moderate shaking	Severe shaking	Rigors ≤ 2 hours	Rigors > 2 hours
Alopecia	___	Thinning of hair	Patchy loss of hair	Complete hair loss