STATISTICAL ANALYSIS PLAN

Study Title:	A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine
Name of Test Drug:	Emtricitabine (FTC)
Study Number	GS-US-162-0112
Protocol Version (Date)	Amendment 1 (24 July 2013)
Analysis Type	Final
Analysis Plan Version:	1.0
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Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ARV	antiretroviral
FTC	emtricitabine
HIV-1	human immunodeficiency virus (Type 1)
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

1. INTRODUCTION

GS-US-162-0112 is an open-label, non-randomized rollover study that will provide FTC-203 study participants enrolled at two study centers in South Africa with continued access to the study drug, emtricitabine, following the completion of the FTC-203 study.

This document describes the statistical analysis methods and data presentations to be used in the summary and analysis of data for Study GS-US-162-0112.

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

1.2. Study Design

1.2.1. Design Configuration

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 at two study centers, representing the maximum possible enrollment in this protocol.

1.2.2. Subject Population

HIV-1 infected pediatric subjects enrolled in FTC-203 at two study centers in South Africa who wish to continue to receive the study drug, emtricitabine, beyond completion of the FTC-203 study were eligible for enrollment. Subjects must have completed at least 96 weeks on the FTC-203 study and were required to complete the End-of-Study Visit for FTC-203 prior to transitioning into the rollover protocol.

1.2.3. Treatment Group

This is an open-label, single-arm study. All subjects were enrolled and treated with emtricitabine, administered in combination with other antiretroviral medications.

Emtricitabine is given as 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 were administered at the dose or doses recommended by the manufacturer in the relevant product/package insert for the treatment of pediatric patients.

1.2.4. Key Eligibility Criteria

Current FTC-203 study participants were eligible to participate in this rollover protocol if

1) they completed all End-of-Study Visit procedures for the FTC-203 study, and

2) either

   a. they had 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 was > 400 copies/mL at the End-of-Study Visit, their viral load was < 1.0 $\log_{10}$ above the nadir recorded after Week 8 of the FTC-203 study and there was reliable genotypic evidence showing a lack of resistance to emtricitabine.

1.2.5. Study Periods/Phases and Duration

Each eligible subject electing to participate in the rollover protocol continued to receive emtricitabine, in combination with other antiretroviral medications, for as long as they continued 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.

1.2.6. Schedule of Assessments

Study procedures at screening, baseline, and during the study are outlined in the protocol and presented in Appendix 1 of the Statistical Analysis Plan (SAP).

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.

2. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

2.1. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who are enrolled into the study. This is the analysis set for all listings.

2.2. Safety Analysis Set

The safety analysis set will include all enrolled subjects who have received at least 1 dose of study drug.

2.3. Subject Grouping

Subjects will be grouped to one group: emtricitabine (FTC).

2.4. Analysis Windows

Study Day 1 is defined as the day when the first dose of study drug in this study, as recorded on the study drug accountability case report form. Baseline visit is defined as the Study Day 1 visit.

Study Day is calculated relative to Study Day 1. For events that occurred on or after Study Day 1, Study Day is calculated as (visit date minus date of the first dose plus 1). For events that occurred prior to Study Day 1, Study Day is calculated as (visit date minus date of the first dose).

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows (for height, weight, AE visits, etc) are presented in Table 2-1.

Table 2-1. Analysis Windows

	Nominal Day	Visit Window
Baseline		≤ 1
Week 12	84	[2, 126]
Week 12*k, k = 2, 3, …, 43	84*k	[84*k-41, 84*k+42]

3. SUBJECT DISPOSITION

3.1. Subject Enrollment

A listing of enrollment, including investigator name and informed consent date will be provided. Subjects' demographic information (see Section 4) will also be included in this listing.

Subjects who do not meet the inclusion and exclusion criteria will be listed.

3.2. Disposition of Subjects

The summary of subject disposition will be provided. This summary will include the number of subjects enrolled and subjects in the safety analysis set.

In addition, the number and percentage of the subjects in the following categories will be summarized:

- Subjects completing study. These are subjects whose reasons for discontinuation are end of study, or end of rollover study;
- Subjects rolled over to Study GS-US-292-1515;
- Prematurely discontinued study (with summary of reasons for discontinuing study).

The denominator for the percentages of subjects in the above category will be the number of subjects in the safety analysis set.

A data listing of reasons for study drug discontinuation will be provided.

3.3. Study Drug Accountability

Drug accountability data along with subjects' height and weight collected on the same form will be listed.

4. DEMOGRAPHICS

Subject demographic data were not collected for this study but were collected for the FTC-203 study. These data will be obtained by linking the data in FTC-203 using subject ID. Subject demographic data collected in Study FTC-203 (age, sex, ethnic origin) will be summarized for subjects enrolled in Study GS-US-162-0112 using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percentage of subjects for categorical data. Age is calculated as age in years at the baseline visit of this study. The summaries of demographic data will be provided for the safety analysis set.

5. EFFICACY ANALYSIS

No efficacy analyses will be performed as no efficacy endpoints were defined for this study.

6. SAFETY ANALYSIS

6.1. Special Events

Subjects with the following special events (if any) will be listed:

- Subjects with SAE
- Subjects with AE leading to study termination

The AE details (eg, reported AE term , AE start date, end date, relationship to study drug, action taken) were only collected for subjects with AE leading to study termination.

6.2. Hyperpigmentation Assessment

Summaries (number and percentage of subjects) of hyperpigmentation (overall and by body location) will be provided using the safety analysis set. Multiple occurrences will be counted once only per subject in each summary. Hyperpigmentation assessment data will also be listed.

6.3. Baseline Antiretroviral (ARV) Regimen

Baseline ARV regimen for this study will be listed.

Appendix 1. Study Procedures Table

	FTC-203	GS-US-162-0112[1]		
Assessment	**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 of the protocol).
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 Gilead Sciences. 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.