CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-937

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-937	Submission Date(s): 26April2006, 01May2006, 18May2006, 23May2006, 23June2006, 27June2006, 28June2006, 30June2006, 03July2006, and 05July2006
Brand Name	ATRIPLA®
Generic Name	Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate
Reviewer	Jennifer L. DiGiacinto, Pharm.D.
Team Leader	Kellie Reynolds, Pharm.D.
OCPB Division	DCP4
OND Division	DAVP
Applicant(s)	Gilead/BMS
Relevant IND(s)	IND 71,420
Submission Type; Code	Fast Track/Priority (1P)
Formulation; Strength(s)	Efavirenz 600-mg/Emtricitabine 200-mg/ Tenofovir disoproxil fumarate 300-mg Combination Tablet
Indication	Treatment of HIV infection

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Gilead® and BMS® submit a New Drug Application (NDA) for a fixed-dose combination (FDC) tablet containing 600 mg efavirenz (EFV), 200 mg emtricitabine (FTC), and 300 mg tenofovir disoproxil fumarate (TDF). EFV is a non-nucleoside reverse transcriptase inhibitor (NNRTI), FTC is a nucleoside reverse transcriptase inhibitor (NRTI), and TDF is a nucleotide reverse transcriptase inhibitor (NtRTI). All three drugs are currently approved as separate formulations for the treatment of HIV infection and FTC/TDF is approved as a combination tablet (CT) for the treatment of HIV infection in adults at least 18 years of age. The applicants have developed a new triple combination tablet (CT) combining all three compounds into a single — tablet (— In support of this NDA, the Applicant adequately addressed the following issues:

- The triple CT is BE to the currently marketed EFV 600-mg tablet (Sustiva®), FTC 200-mg capsule (Emtriva®), and TDF 300-mg tablet (Viread®), when the three single products are administered together.
- Since the applicant(s) did not conduct a food effect study, the new triple CT tablet should be taken on an empty stomach once daily. The lack of a food effect study is acceptable because the Sustiva® label indicates that Sustiva® should be taken on any empty stomach. Emtriva® and Viread® can be taken with or without food.

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant(s) is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

EFV, FTC, and TDF are co-formulated as a single — containing 600-mg EFV, 200-mg of FTC, and 300-mg of TDF, which will be administered in a fasted state once daily as a complete antiretroviral regimen and also as part of an antiretroviral regimen. This NDA contains a pivotal BE study (GS-US-177-0105).

GS-US-177-0105 is the pivotal bioequivalence (BE) study that compares the new triple CT of EFV/FTC/TDF to a Sustiva® tablet, an Emtriva® capsule, and a Viread® tablet administered as separate formulations in fasted healthy subjects. This was a Phase 1, randomized, single-dose, open-label, two-way cross-over pharmacokinetic (PK) study in 48 healthy volunteers. A total of 45 subjects completed the study. The results of this pivotal BE study demonstrate that the administration of EFV/FTC/TDF triple CT results in plasma-concentration-time profiles of EFV, FTC, and TDF similar to those after the concurrent administration of the three separate formulations. The FDA Bioavailability (BA) and BE Studies for Orally Administered Drug Products Guidance indicates BE is concluded if the 90% CI for the ratio (test to reference) falls within 80% to 125% for C_{max} and AUC_{0-t} and AUC_{0-inf}. EFV/FTC/TDF triple CT (test product) met the BE definition when compared to the separate formulations of EFV, FTC, and TDF (reference products). See table below.

Geometric Least Square Mean Ratios and 90% Confidence Interval (CI) for EFV/FTC/TDF Administered as the Combination Tablet and Marketed Formulations Concurrently (GS-US-177-0105)

EFV	Geometric Least Square Mean Ratio (90%)		
EFV/FTC/TDF CT	C_{max}	AUC_{0-t}	AUC_{0-inf}
EFV + FTC + TDF	99.89 (93.37, 106.88)	95.73 (90.50, 101.26)	95.19 (88.9, 101.91)
FTC	**Geometric Least Square Mean Ratio (90%)**		
EFV/FTC/TDF CT	C_{max}	AUC_{0-t}	AUC_{0-inf}
EFV + FTC + TDF	88.84 (84.02, 93.94)	97.98 (94.90, 101.16)	97.96 (94.86, 101.16)
TDF	**Geometric Least Square Mean Ratio (90%)**		
EFV/FTC/TDF CT	C_{max}	AUC_{0-t}	AUC_{0-inf}
EFV + FTC + TDF	91.46 (84.64, 98.83)	99.29 (91.02, 108.32)	100.45 (93.22, 108.23)

Data Source: Table from Module 5.3.1.2, GS-US-177-0105 Clinical Study Report, Section 11.1, Table 6.

The dissolution of EFV/FTC/TDF triple CT is assessed using USP II Apparatus with paddles operated at 100 ± 4 rpm. The dissolution medium is 1000 mL of 2% sodium lauryl sulfate (SLS) in water maintained at 37 ± 0.5°C. The amounts of EFV, FTC, and TDF dissolved are determined by reversed-phase HPLC method (TM-053). The single time-point specification of dissolved at 30 minutes is proposed for EFV/FTC/TDF triple tablets (Q= dissolved in 30 minutes). For a complete dissolution report, please review Dr. George Lunn's chemistry review for this NDA.

The applicant(s) proposed a specification of dissolved at 30-minutes. The proposed dissolution method and specification for are acceptable.

Because the pivotal BE study is the primary basis of approval of NDA 21-937, an inspection of the clinical trial site and the analytical laboratory site was conducted by the Division of Scientific Investigations (DSI). The findings of the DSI inspections included two 483's that were issued at the clinical site in and seven (7) 483's that were issued at the analytical site in Durham, NC (Gilead Sciences, Inc.). A brief summary of the 483's issued can be found below; however, for a more detail discussion about these 483's, please see the DSI review by Dr. Martin Yau.

The two clinical site 483's that were issued included a delay in reporting a spontaneous abortion to the Sponsor within the pre-specified time-frame of 24 hours for all serious adverse events (SAEs) and a protocol deviation of pre-dose blood draws occurring after the dose was given in two subjects. Both 483's were considered to have minimal impact on study results.

The seven analytical site 483's that were issued included the following observations:

- **Observation 1:** The failure to reject an analytical run when > 50% of the quality control (QC) samples fail at the same level.
- **Observation 2:** Review of the tenofovir and emtricitabine analytical runs found some inconsistencies in run acceptance/rejection when QC's failed for one of the analytes.
- **Observation 3:** Failure to include all QC results in the determination of

assay accuracy and precision.

- **Observation 4:** Failure to properly document the 460 days long term frozen stability study for emtricitabine and tenofovir. There was no written record showing that the stability samples were stored at -80°C for 460 days.

- **Observation 5:** Many study samples were re-assayed for efavirenz, emtricitabine, and tenofovir due to PK reasons. No objective criteria were established a priori to justify selection of these study samples.

- **Observation 6:** Failure to conduct study to demonstrate the lack of matrix effect in the emtricitabine and tenofovir LC/MS/MS assay.

- **Observation 7:** Review of temperature charts/alarm records for freezers 12 and 13 (used to store plasma samples from study GS-US-177-0105) found significant variation in temperatures and alarms being triggered.

The Applicant has provided responses for all 483's issued and we feel they have provided the appropriate documentation to resolve the 483's issued during the DSI inspection. In particular, Observation 5 resolution required the Applicant to re-run the BE analysis for all three drug components using the original concentration values and compare these results to the BE analysis results they submitted in the NDA that were calculated using the re-assayed values. As demonstrated in the table below, use of the initial laboratory data does not alter the conclusion of BE on the fixed-dose combination to the individual dosage forms.

Geometric Least Square Mean Ratios and 90% Confidence Interval (CI) for EFV/FTC/TDF Administered as the Combination Tablet and Marketed Formulations Concurrently (GS-US-177-0105) Using the Original Concentrations for BE Analysis

EFV	**Geometric Least Square Mean Ratio (90%)**		
EFV/FTC/TDF CT	C_{max}	AUC_{0-t}	AUC_{0-inf}
EFV + FTC + TDF	100 (93.5, 107)	96.8 (91.3, 103)	95 (88.5, 102)
FTC	**Geometric Least Square Mean Ratio (90%)**		
EFV/FTC/TDF CT	C_{max}	AUC_{0-t}	AUC_{0-inf}
EFV + FTC + TDF	88.8 (84, 93.9)	97.8 (94.7, 101)	97.8 (94.7, 101)
TDF	**Geometric Least Square Mean Ratio (90%)**		
EFV/FTC/TDF CT	C_{max}	AUC_{0-t}	AUC_{0-inf}
EFV + FTC + TDF	91.5 (84.6, 98.8)	99.3 (91., 108)	100 (93.2, 108)

2. QUESTION BASED REVIEW (See NDA 21-500 and NDA 21-356 for section 2.1 through 2.4 information)

2.1 General Attributes of the Drug

For detailed information regarding the triple combination tablet formulation development, please refer to the 'Formulation Development' section in the GS-US-177-0105 pivotal BE study report located in the Appendices.

2.2 General Clinical Pharmacology

Not applicable.

2.3 Intrinsic Factors

Not applicable.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed EFV/FTC/TDF CT formulation to the EFV, FTC, and TDF currently marketed formulations in terms of comparative exposure?

The clinical EFV/FTC/TDF triple CT used in the pivotal BE study (GS-US-177-0105) and the proposed commercial formulation of EFV/FTC/TDF triple CT are identical. GS-US-177-0105 compares the new triple CT of EFV/FTC/TDF to EFV, FTC, and TDF as separate formulations administered concurrently. The products are BE under fasted conditions.

The geometric least square (GLS) mean test to reference ratio and 90% CI values for EFV are listed below.

90% Confidence Interval for Geometric Mean Ratios of EFV PK Parameters for Test versus Reference

Efavirenz PK Parameter[a]	Geometric Least Squares Means[b]		Geometric Least Squares Mean Ratio (%)	90% CI
	Test (N = 44)	Reference (N = 44)		
C_{max} (ng/mL)	2190.20	2192.55	99.89	93.37, 106.88
$AUC_{0\text{-}last}$ (ng•h/mL)	120841.0	126231.3	95.73	90.50, 101.26
AUC_{inf} (ng•h/mL)	137106.6	144030.3	95.19	88.92, 101.91

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for efavirenz. In addition, Subject 46 did not meet the pharmacokinetic analysis criteria and was excluded from the pharmacokinetic analysis set for efavirenz.

b Geometric least-squares means are obtained by the back-transformation of least-squares means of the parameters based on the natural logarithmic scale.

Source: Module 5.3.1.2, GS-US-177-0105 Clinical Study Report, Section 11.1, Table 6

APPEARS THIS WAY
ON ORIGINAL

The GLS mean test to reference ratio and 90% CI values for FTC are listed below.

90% Confidence Interval for Geometric Mean Ratios of FTC PK Parameters for Test versus Reference

Emtricitabine PK Parameter[a]	Geometric Least Squares Means[b]		Geometric Least Squares Mean Ratio (%)	90% CI
	Test (N = 45)	Reference (N = 45)		
C_{max} (ng/mL)	2066.48	2325.96	88.84	84.02, 93.94
AUC_{t-last} (ng•h/mL)	10523.63	10740.76	97.98	94.90, 101.16
AUC_{inf} (ng•h/mL)	10694.43	10916.96	97.96	94.86, 101.16

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for emtricitabine.

b Geometric least squares means are obtained by the back-transformation of least-squares means of the parameters based on the natural logarithmic scale.

Source: Module 5.3.1.2, GS-US-177-0105 Clinical Study Report, Section 11.1, Table 6

The GLS mean test to reference ratio and 90% CI values for tenofovir (TNF) are listed below.

90% Confidence Interval for Geometric Mean Ratios of TNF PK Parameters for Test versus Reference

Tenofovir PK Parameter[a]	Geometric Least-Squares Means[b]		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test (N = 45)	Reference (N = 45)		
C_{max} (ng/mL)	307.25	335.93	91.46	84.64, 98.83
AUC_{t-last} (ng•h/mL)	1845.03	1858.15	99.29	91.02, 108.32
AUC_{inf} (ng•h/mL)	2218.24	2208.41	100.45	93.22, 108.23

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for tenofovir.

b Geometric least-squares means are obtained by the back-transformation of least-squares means of the parameters based on the natural logarithmic scale.

Source: Section 11.1, Table 6

2.5.2 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

The pivotal BE study, GS-US-177-0105 did not study the food effect with the new triple CT. The recommended administration of EFV is on an empty stomach because of the significant increases seen in C_{max} and AUC levels when taken with either a high-fat, high caloric meal or a low-fat, low caloric meal. These increased concentrations have been linked to an increase in CNS adverse reactions (ADRs) reported with the use of EFV. FTC and TDF can be taken without regard to food. Since EFV has to be taken on an empty stomach, no food effect study was required.

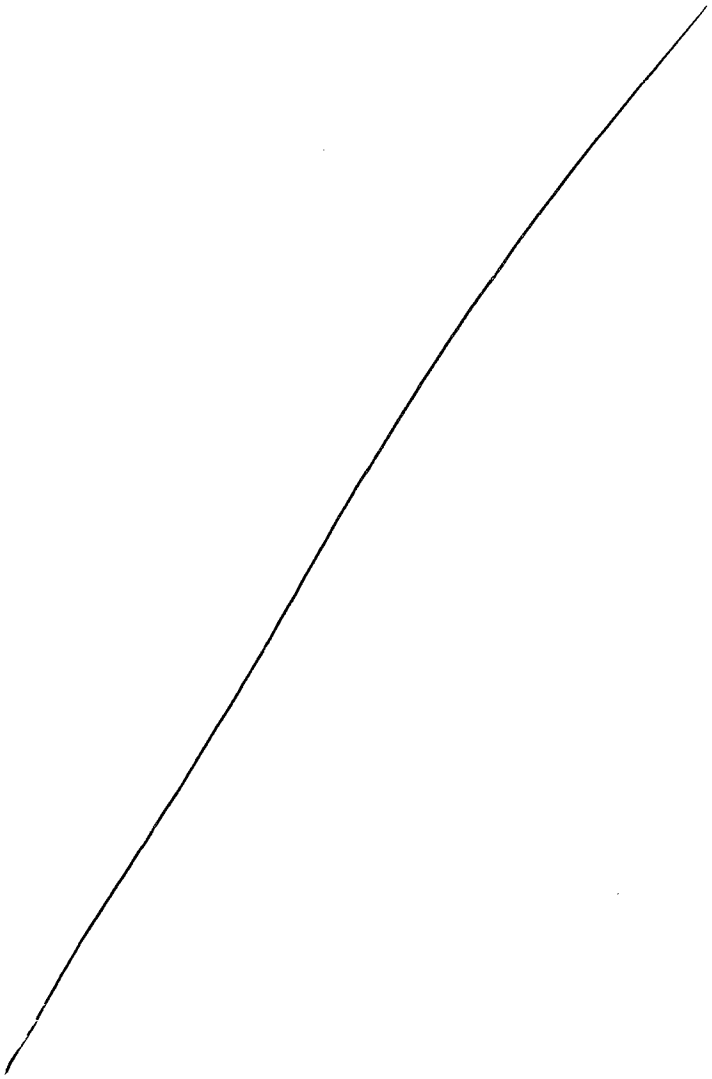
The EFV/FTC/TDF triple CT must be taken on an empty stomach.

2.5.3 *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

Please refer to the chemistry review by Dr. George Lunn for the complete dissolution discussion.

2.6 Analytical Section
Analytical methods were acceptable (See Individual Study Review).

3. ATRIPLA® LABELING RECOMMENDATIONS



24 Page(s) Withheld

_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

√ § 552(b)(4) Draft Labeling

Jennifer L. DiGiacinto, Pharm.D.
Senior Reviewer, Clinical Pharmacology
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Products Section
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc: HFD-530 /NDA 21-937
/MO/Fleischer
PM/Holloman
/JDiGiacinto
/TL/KReynolds

4. Appendices

4.1 Individual Study Reviews

4.1.1 Bioavailability & Bioequivalence Studies

Pivotal BE Study (GS-US-177-0105)

Background
The FDA approved efavirenz (EFV) for the treatment of HIV-1 infection on 17September1998 as a capsule formulation (NDA 20-972) and on 01February2002 as a tablet formulation (NDA 21-360). EFV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is marketed under the brand name Sustiva® as hard gelatin capsules (50-, 100-, and 200-mg) and 600-mg film-coated tablets, for once daily administration. Emtricitabine (FTC) received its first approval for treatment of HIV-1 infection on 02July2003 (NDA 21-500) as an oral capsule for use in adults and on 28September2005 as an oral solution for use in patients over 3 months of age (NDA 21-896). FTC is a nucleoside reverse transcriptase inhibitor (NRTI) that is marketed under the brand name Emtriva® as a once daily administration (200-mg capsule or 10 mg/mL an oral solution). The FDA approved tenofovir disoproxil fumarate (TDF) for the treatment of HIV-1 infection on 26October2001 as a 300-mg tablet formulation (NDA 21-356). TDF, the oral prodrug of tenofovir, is a nucleotide reverse transcriptase inhibitor (NtRTI) approved as a once daily administration. TDF is marketed under the brand name Viread®. Truvada®, the once daily, film-coated combination tablet of FTC (200-mg) and TDF (300-mg) was approved in the US on 02August2004 (NDA 21-752).

Non-adherence is a major issue for patients taking antiretroviral therapy (ART). The estimated non-adherence rate for HIV treatment ranges between 50-70%. It is well documented in the literature that adherence rates < 80% are associated with detectable viremia in a majority of patients. Factors that contribute to non-adherence include pill burden, adverse events (ADEs), drug-drug interactions, and drug-food interactions. In an attempt to decrease the pill burden, the applicant's have combined three previously approved ART drugs (EFV/FTC/TDF) into a single combination tablet (CT) with the intent to simplify ART regimens and to improve patient adherence.

GS-US-177-0105 is the pivotal bioequivalence (BE) study that compares the new triple CT of EFV/FTC/TDF to the individual EFV, FTC, and TDF formulations administered concurrently.

Formulation Development
In developing the triple CT, the applicant developed a total of 5 formulations. BE studies were conducted on all 5 formulations. All studies are completed with the exception of the Formulation 4 study. The initial approach involved developing a co-granulation of EFV, FTC, and TDF and compressing them into a single layer tablet (i.e., Formulation 1).

- **Formulation 1 (GS-US-177-0101):** failed to demonstrate BE for EFV due to significantly lower AUC and C_{max} levels than those obtained with the commercial formulation of Sustiva® tablets. Both FTC and TDF components of the triple CT were BE to the corresponding commercial formulations, Emtriva® capsules and Viread® tablets, respectively.

Formulation Development Continued
The second approach consisted of a [redacted]

[redacted] (i.e., Formulation 2).

- **Formulation 2 (GS-US-185R-0102):** significantly increased the EFV absorption or AUC compared to Formulation 1, but still did not demonstrate BE for EFV compared to the Sustiva® tablet. FTC and TDF were BE to the commercial formulations Emtriva® capsules and Viread® tablets, respectively.

The third approach involved a [redacted]

[redacted] proposed commercial formulation)).

- **Formulation 3 (GS-US-177-0103):** significantly increased EFV absorption compared to Formulation 2 and was equivalent to the Sustiva® tablet formulation in terms of AUC, but with respect to C_{max} the concentrations were lower. FTC and TDF exposure levels from Formulation 3 were BE to the commercial Emtriva® capsules and Viread® tablets, respectively.

- **Formulation 4 (GS-US-177-0104):** The results for the clinical BE study GS-US-177-0104 are pending.

- **Formulation 5 (Pivotal BE GS-US-177-0105):** The results from this clinical BE study demonstrate that the proposed commercial formulation for the triple CT (Formulation 5) was BE to the commercial formulation of Sustiva® tablets, Emtriva® capsules, and Viread® tablets, respectively. The decision was made to select Formulation 5 as the commercial formulation to market.

The table below summarizes all the modifications to each formulation throughout the development of the triple CT.

EFV/FTC/TDF Combination Tablet Development Summary

Formulation Number	Clinical Protocol Number	Significant Formulation Change/ Reason for Change	Effect of Change
Development Formulation 1	GS-US-177-0101	Initial formulation	With this initial investigational formulation, EFV did not meet the criteria for bioequivalence to the innovator product. TDF and FTC were bioequivalent to the innovator products.
Development Formulation 2	GS-US-185R-0102	Formulation was changed from a	C_{max} and AUC of EFV increased compared with Formulation 1; however, EFV was still not bioequivalent to the innovator product. TDF and FTC were bioequivalent to the innovator products.
Development Formulation 3	GS-US-177-0103	Formulation 2 was changed from a	C_{max} and AUC of EFV increased compared with Formulations 1 and 2; however, the EFV was still not bioequivalent (i.e., C_{max}) to the innovator product. TDF and FTC were bioequivalent to the innovator products.
Proposed Commercial Formulation	GS-US-177-0105		C_{max} and AUC of EFV increased compared with Formulations 1, 2, and 3, and EFV was bioequivalent to the innovator product. TDF and FTC were bioequivalent to the innovator products.

Study Objectives

Primary-

- Evaluate the BE of a fixed-dose CT (containing 600-mg EFV, 200-mg FTC, and 300-mg TDF) to a single 600-mg tablet of EFV, a 200-mg capsule of FTC, and a 300-mg tablet of TDF taken concurrently under fasted conditions.

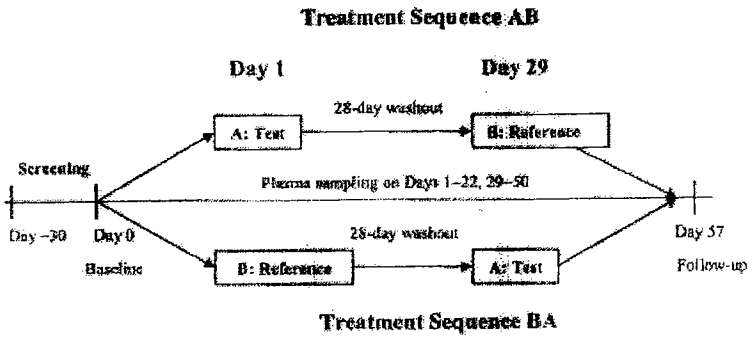
Secondary-

- Assess the safety of EFV, FTC, and TDF when administered together either as a combination tablet or as individual dosage forms.

Study Design

This was a Phase 1, randomized, single-dose, open-label, two-way cross-over pharmacokinetic (PK) study in healthy volunteers that evaluated the BE of EFV/FTC/TDF triple CT compared to EFV, FTC, and TDF administered concurrently as the individual drug products to healthy adult volunteers in a fasted state. The planned enrollment was 48 healthy male and female subjects with the goal of obtaining 38 evaluable PK subjects. A total of N=45 subjects completed the study. The three patients that did not complete the study will be discussed in the demographics section. A 28-day washout period separated each treatment period.

Study Schema



Study Demographics

Characteristic	Total (N=48) N (%)
Gender:	
M	13(27)
F	35(73)
Race:	
White	3(6)
Black	1(2)
American Indian	1(2)
Hispanic	43(90)
Age:	
Mean (SD)	30 (7.1)
Median	30
Min, Max	18, 45
Height at Screening (cm)	
Mean (SD)	163.3 (8.01)
Median	161.0
Min, Max	151.6, 184.4
Weight at Screening (kg)	
Mean (SD)	65.2 (7.15)
Median	64.8
Min, Max	45.7, 81.1

- In Study GS-US-177-0105, subjects enrolled were healthy male and healthy, non-pregnant female subjects between the ages of 18 and 45 years of age. A total of 48 subjects were enrolled with three dropouts. Three subjects dropped out in the first period; two female subjects dropped out due to pregnancy and one male subject due to a positive drug screen test during the study. Both female subjects experienced spontaneous abortions; the first subject on Day 78 (Subject 9, 39 year old Hispanic woman) and the second subject (Subject 13, 22 year old Hispanic woman) a spontaneous abortion was confirmed with a negative serum hCG level conducted on Day 57. For further discussion about these three dropouts, please see Mr. Russ Fleischer's clinical review.

Study Treatments

- Treatment A **(Test Treatment)**: EFV/FTC/TDF (600-mg EFV/200-mg FTC/300-mg TDF) single fixed-dose triple CT administered in a fasted state.
- Treatment B **(Reference Treatment)**: EFV + FTC + TDF (600-mg Sustiva® tablet/200-mg Emtriva® capsule/300-mg Viread® tablet) taken concurrently and administered in a fasted state.

Test/Reference Products and Lot #s

- **Test Product:** Triple CT of EFV/FTC/TDF (600-mg/200-mg/300-mg), Lot # AA511B1, Batch size — which corresponds to — tablets.

- **Reference Product: Sustiva®,** single tablet of 600-mg EFV, Lot# ETE299A/ **Emtriva®**, single capsule of FTC (200-mg), Lot # 13319AF22/**Viread®**, single tablet of TDF (300-mg), Lot # FBK261.

Batch Formula for Commercial Formulation

EFV/FTC/TDF CT are — and have dimensions of approximately 20.0 mm x 10.4 mm (length x width). The manufacturing formula for a typical commercial batch of — (corresponding — tablets) is given in the table below.

Batch Formula for EFV/FTC/TDF Tablets

Component	Reference to Quality Standard	Amount (kg) per batch[1]
Efavirenz	In-house Standard	
Croscarmellose Sodium	NF	
Microcrystalline Cellulose	NF	
Hydroxypropyl Cellulose	NF	
Sodium Lauryl Sulfate	NF	
Magnesium Stearate	NF	
—	—	
Emtricitabine		
Tenofovir Disoproxil Fumarate		
—		
Film Coating		
	In-house Standard	
—	—	
Total Batch Size (Coated Tablets)		

PK Sampling

Serial blood samples for the determination of plasma EFV, FTC, and TNF concentrations were collected at pre-dose (time 0) and then 0.25, 0.5, 0.75, 1, 1.5, 2,

2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 240, 336, and 504 hours post-dose on Days 1 and 29.

PK Data Analysis

- The PK parameters for EFV, FTC, and TNF were assessed using noncompartmental methods (WinNonlin Professional Edition, Version 5.0.1, Pharsight Corporation).
- All pharmacokinetic parameters for BE treatment arms were analyzed using analysis of variance (ANOVA) using SAS PROC MIXED.
- For the assessment of formulation BE, a 90% CI was obtained for the geometric mean ratio (Treatment A as test product and Treatment B as reference product).
- BE was concluded if the 90% CI intervals were within the 80-125% range for C_{max} and AUC.

GS-US-177-0105 Assay Validation

Concentrations of EFV, FTC, and TNF in human plasma samples collected during GS-US-177-0105 were determined using Good Laboratory Practice methods (GLP) and a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) bioanalytical method. The assays for EFV, FTC, and TNF were performed by the Gilead Bioanalytical Laboratory (Durham, NC, USA). All samples for an individual subject were analyzed on a single run to minimize assay-dependent variability. The assay characteristics for this study are listed below.

Parameter	EFV	FTC	TNF
Linear Range (ng/mL)	5 to 5000	5 to 3000	10 to 1000
LLOQ (ng/mL)	5	5	10
Stability-freeze-thaw (days)	532	460	460
Inter-Assay Precision Range[a]	3.5% to 13.0%	4.0% to 9.5%	4.4% to 7.9%
Intra-Assay Precision Range[a]	1.5% to 12.0%	2.44% to 7.44%	2.24% to 8.33%
Inter-Assay Accuracy Range[b]	-4.5% to 2.8%	-1.7% to 8.0%	-5.2% to 4.0%
Intra-Assay Accuracy Range[b]	-15.7% to 8.0%	-2.0% to 1.5%	-2.0% to 8.1%

[a] Relative Standard Deviation

[b] Difference for nominal concentrations

The precision and accuracy in the assay validation were evaluated using 3 separate analytical runs each containing quality control (QC) samples (N=4) in replicates of 5 for FTC and TDF and replicates of 6 for EFV.

Reviewer Comment: The assay is acceptable.

Reassayed Samples

EFV

There were 16 subjects that had a combined total of 19 samples reassayed. The applicant states these samples were reassayed due to initial 'questionable results'. The final values reported were either reported as the mean of reassayed values reported in accordance with SOP-BA-28018 or the initial value reported in accordance with SOP-BA-28018.

FTC

There were 12 subjects that had a combined total of 20 samples reassayed. The applicant states these samples were reassayed due to initial dilution errors (AQL) or

initial 'questionable results'. The final values reported were either reported as the reassayed value reported in accordance with SOP-BA-28018, the mean of reassayed values reported in accordance with SOP-BA-28018, the initial value reported in accordance with SOP-BA-28018, or not reported in accordance with SOP-BA-28018.

TDF

There were 8 subjects that had a combined total of 13 samples reassayed. The applicant states these samples were reassayed due initial 'questionable results'. The final values reported were either reported as the reassayed value reported in accordance with SOP-BA-28018, the mean of reassayed values reported in accordance with SOP-BA-28018, the initial value reported in accordance with SOP-BA-28018, or not reported in accordance with SOP-BA-28018.

Reviewer Comment: The applicant followed SOP for all reassayed samples. The reported reassayed samples do not impact study results.

Protocol Violations

Not Following Study Procedures

There were two deviations of subjects not following study procedures. Subject 9, who had a positive hCG test on Day 8, was using only one method of birth control (condoms) at the time of conception. Subject 43 did not answer a question on Day 7 about whether he had donated plasma.

Taking Prohibited Agents

Six deviations of subjects taking prohibited agents were reported. Subject 42 tested positive for amphetamines on Day 28 and was withdrawn from the study. Five other subjects (Subjects 42, 15, 19, 32, and 34) took prohibited concomitant medications while in the study. These prohibited medications were diphenhydramine, ibuprofen, and a topical cream (Cuatroderm®).

Reviewer Comment: The protocol violations that are reported above do not impact the study results.

GS-US-104-172 Study Results

The summary statistics of EFV PK parameters are listed below.

Summary of EFV PK Parameters

Efavirenz PK Parameter[a]	Test Treatment (N = 44)	Reference Treatment (N = 44)
C_{max} (ng/mL) mean (%CV)	2276.4 (26.7)	2298.5 (30.6)
T_{max} (h) median (min, max)	3.50 (2.00, 8.00)	3.75 (1.50,5.50)
C_{last} (ng/mL) mean (%CV)	52.5 (63.6)	70.1 (64.4)
T_{last} (h) median (min, max)	504.1 (240.0, 505.1)	504.2 (240.0, 504.8)
AUC_{0-last} (ng•h/mL) mean (%CV)	125040.7 (25.9)	132784.4 (27.3)
AUC_{inf} (ng•h/mL) mean (%CV)	143601.8 (32.0)	155309.5 (35.1)
$\%AUC_{exp}$ mean (%CV)	11.3 (66.3)	12.3 (67.6)
$T_{½}$ (h) median (min, max)	164.4 (59.8, 532.6)	166.1 (43.0, 381.2)

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for efavirenz. In addition, Subject 46 did not meet the pharmacokinetic analysis criteria and was excluded from the pharmacokinetic analysis set for efavirenz.

Source: Section 11.1, Table 5

The geometric least square means (GLS) and 90% CI values for EFV are listed below.

90% Confidence Interval for Geometric Mean Ratios of EFV PK Parameters for Test versus Reference

Efavirenz PK Parameter[a]	Geometric Least Squares Means[b]		Geometric Least Squares Mean Ratio (%)	90% CI
	Test (N = 44)	Reference (N = 44)		
C_{max} (ng/mL)	2190.20	2192.55	99.89	93.37, 106.88
AUC_{0-last} (ng•h/mL)	120841.0	126231.3	95.73	90.50, 101.26
AUC_{inf} (ng•h/mL)	137106.6	144030.3	95.19	88.92, 101.91

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for efavirenz. In addition, Subject 46 did not meet the pharmacokinetic analysis criteria and was excluded from the pharmacokinetic analysis set for efavirenz.

b Geometric least-squares means are obtained by the back-transformation of least-squares means of the parameters based on the natural logarithmic scale.

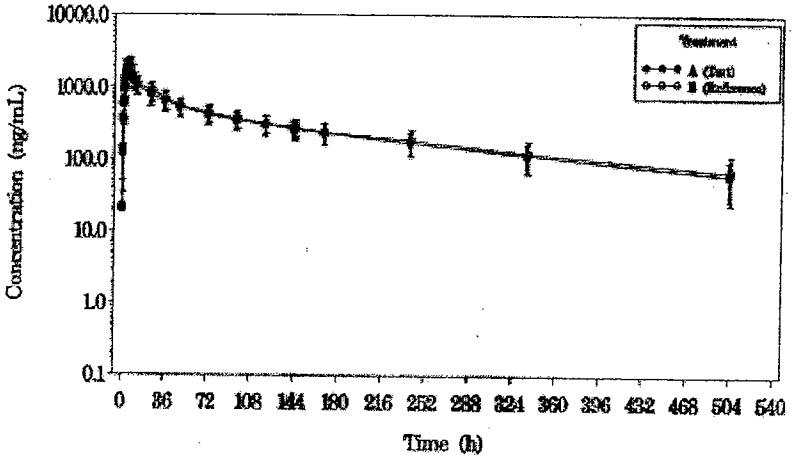
Source: Module 5.3.1.2, GS-US-177-0105 Clinical Study Report, Section 11.1, Table 6

Reviewer Comment: *Study Subject 46 had a pre-dose EFV concentration in Period 2 that was ≥ 5% of the subject's C_{max}; therefore, per FDA guidance for BA and BE studies, the subject did not meet the PK analysis criteria for EFV and was excluded from the PK analysis set for EFV.*

APPEARS THIS WAY
ON ORIGINAL

The plasma concentration-time profile of EFV after administration of the Test or Reference Treatment to 504 hours is listed below.

Plasma Concentration-Time Profile of EFV after Administration of the Test or Reference Treatment in Study GS-US-177-0105



Test Treatment = EFV/FTC/TDF fixed-dose triple-combination tablet

Reference Treatment = EFV + FTC + TDF taken concurrently under fasted conditions

Values presented as mean ± SD. Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for efavirenz. In addition, Subject 46 did not meet the pharmacokinetic analysis criteria and was excluded from the pharmacokinetic analysis set for efavirenz.

Source: Section 11.1, Figure 2

The summary statistics of FTC PK parameters are listed below.

Summary of FTC PK Parameters

Emtricitabine PK Parameter[a]	Test Treatment (N = 45)	Reference Treatment (N = 45)
C_{max} (ng/mL) mean (%CV)	2130.6 (25.3)	2384.4 (20.4)
T_{max} (h) median (min, max)	1.50 (1.00, 5.00)	1.50 (0.77, 2.50)
C_{last} (ng/mL) mean (%CV)	8.5 (29.4)	8.8 (41.8)
T_{last} (h) median (min, max)	48.2 (36.0, 504.6)	48.2 (36.0, 96.2)
AUC_{0-last} (ng·h/mL) mean (%CV)	10682.6 (18.1)	10674.4 (14.9)
AUC_{inf} (ng·h/mL) mean (%CV)	10854.9 (17.9)	11054.3 (14.9)
$\%AUC_{exp}$ mean (%CV)	1.6 (58.2)	1.6 (59.8)
$T_{½}$ (h) median (min, max)	10.6 (5.9, 47.5)	11.4 (6.6, 38.1)

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for emtricitabine.

Source: Section 11.1, Table 5

The GLS and 90% CI values for FTC are listed below.

90% Confidence Interval for Geometric Mean Ratios of FTC PK Parameters for Test versus Reference

Emtricitabine PK Parameter[a]	Geometric Least Squares Means[b]		Geometric Least Squares Mean Ratio (%)	90% CI
	Test (N = 45)	Reference (N = 45)		
C_{max} (ng/mL)	2066.48	2325.96	88.84	84.02, 93.94
AUC_{0-last} (ng•h/mL)	10523.83	10740.78	97.98	94.90, 101.16
AUC_{Inf} (ng-h/mL)	10694.43	10916.98	97.96	94.86, 101.16

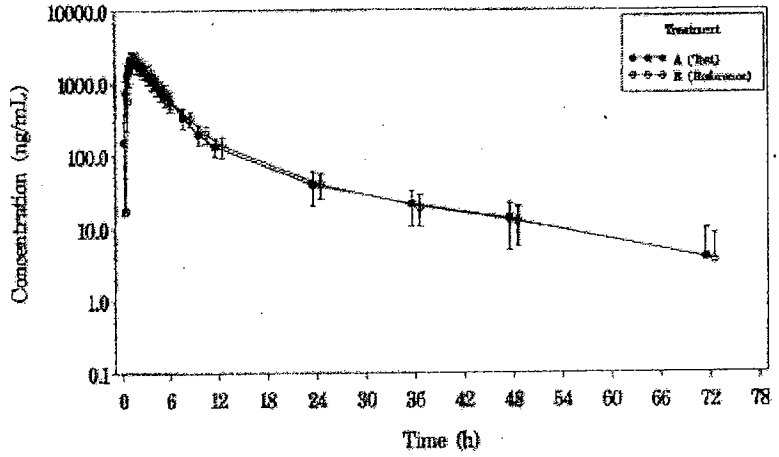
a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for emtricitabine.

b Geometric least squares means are obtained by the back-transformation of least-squares means of the parameters based on the natural logarithmic scale.

Source: Module 5.3.1.2, GS-US-177-0105 Clinical Study Report, Section 11.1, Table 6

The plasma concentration-time profile of FTC after administration of the Test or Reference Treatment to 76 hours is listed below.

Plasma Concentration-Time Profile of FTC after Administration of the Test or Reference Treatment in Study GS-US-177-0105



Test Treatment = EFV/FTC/TDF fixed-dose triple-combination tablet

Reference Treatment = EFV + FTC + TDF taken concurrently under fasted conditions

Values presented as mean ± SD. Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for efavirenz. No plasma concentration values for emtricitabine were quantifiable beyond 96 hours except for a detectable concentration at 504 hours for Subject 36.

Source: Section 11.1, Figure 2

APPEARS THIS WAY
ON ORIGINAL

The summary statistics of TNF PK parameters are listed below.

Summary of TNF PK Parameters

Tenofovir PK Parameter[a]	Test Treatment (N = 45)	Reference Treatment (N = 45)
C_{max} (ng/mL) mean (%CV)	325.1 (34.2)	352.9 (29.6)
T_{max} (h) median (min, max)	1.00 (0.50, 3.50)	0.75 (0.50, 2.00)
C_{last} (ng/mL) mean (%CV)	13.5 (23.6)	13.6 (18.6)
T_{last} (h) median (min, max)	48.0 (12.0, 72.0)	48.0 (12.0, 72.0)
AUC_{0-last} (ng•h/mL) mean (%CV)	1948.8 (32.9)	1969.0 (32.8)
AUC_{inf} (ng•h/mL) mean (%CV)	2314.0 (29.2)	2319.4 (30.3)
$\%AUC_{extp}$ mean (%CV)	16.7 (35.0)	15.7 (28.6)
$T_{½}$ (h) median (min, max)	18.5 (7.7, 28.4)	17.2 (7.8, 31.4)

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for tenofovir.

Source: Section 11.1, Table 5

The GLS and 90% CI values for TNF are listed below.

90% Confidence Interval for Geometric Mean Ratios of TNF PK Parameters for Test versus Reference

Tenofovir PK Parameter[a]	Geometric Least-Squares Means[b]		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test (N = 45)	Reference (N = 45)		
C_{max} (ng/mL)	307.25	335.93	91.46	84.64, 98.83
AUC_{0-last} (ng•h/mL)	1845.03	1858.15	99.29	91.02, 108.32
AUC_{inf} (ng•h/mL)	2218.24	2208.41	100.45	93.22, 108.23

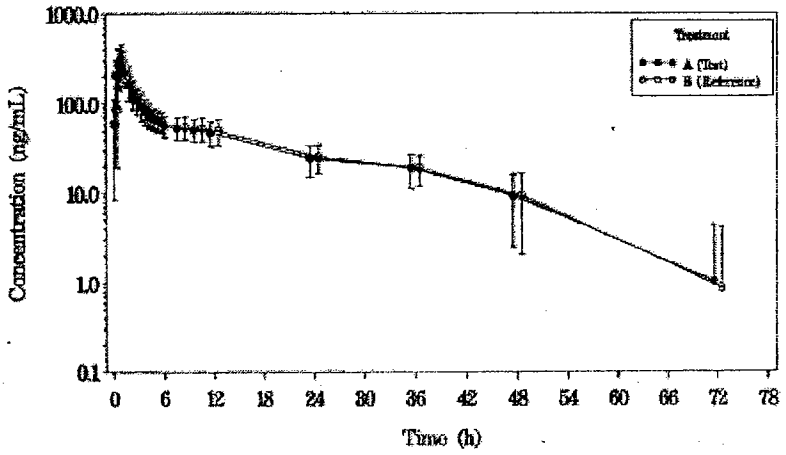
a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for tenofovir.

b Geometric least-squares means are obtained by the back-transformation of least-squares means of the parameters based on the natural logarithmic scale.

Source: Section 11.1, Table 6

The plasma concentration-time profile of TNF after administration of the Test or Reference Treatment to 76 hours is listed below.

Plasma Concentration-Time Profile of TNF after Administration of the Test or Reference Treatment in Study GS-US-177-0105



Test Treatment = EFV/FTC/TDF fixed-dose triple-combination tablet

Reference Treatment = EFV + FTC + TDF taken concurrently under fasted conditions

Values presented as mean ± SD. Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set for tenofovir. No plasma concentration value for tenofovir was quantifiable beyond 72 hours.

Source: Section 11.1, Figure 2

Reviewer Comment: The EFV/FTC/TDF triple CT is BE to the EFV single tablet (Sustiva®), the FTC single capsule (Emtriva®), and the TDF single tablet (Viread®). I conducted a reanalysis of the BE data provided electronically by the Applicant and my results confirm the Applicant's conclusion that the triple CT tab is BE to the three individual drug products when taken in a fasted state.

Assessment/Conclusion

1. EFV/FTC/TDF triple CT is BE to EFV 600-mg tablet, FTC 200-mg capsule, and TDF 300-mg tablet administered as separate formulations in fasted subjects.

2. The EFV/FTC/TDF triple CT should be administered in a fasted state.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer DiGiacinto
7/10/2006 04:37:02 PM
BIOPHARMACEUTICS

Kellie Reynolds
7/11/2006 09:19:34 AM
BIOPHARMACEUTICS