CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202123Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-123	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	February 10, 2011		
Division:	Division of Antiviral Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Gilead Sciences, Inc.	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed-Dose Combination Tablets (FTC/RPV/TDF)	**Date Assigned:**	February 10, 2011
Generic Name:	Emtricitabine/Rilpivirine HCl/ Tenofovir DF	**Date of Review:**	July 14, 2011
Indication:	Treatment of HIV-1 infection in adults	**Type of Submission:** Resubmission of Priority New Drug Application	
Formulation/ strengths	Tablet/ FTC/RPV/TDF 200 mg/25 mg/300 mg		
Route of Administration	Oral		

SUBMISSION:

NDA 202-123 dated February 10, 2011 is a priority resubmission for a fixed-dose combination (FDC) tablet of emtricitabine/ rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF) for the treatment of HIV-1 infection in adults. Emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) are antiretroviral agents of the nucleoside reverse transcriptase inhibitor (N(t)RTI) class developed by Gilead that have been approved for the treatment of HIV-1 infection as stand-alone agents or in fixed-dose combination products with the following trade names: Emtriva®(emtricitabine), Viread®(tenofovir DF), Truvada® (emtricitabine/tenofovir DF), and Atripla® (efavirenz/ emtricitabine/tenofovir DF).

Rilpivirine is an antiretroviral agent of the nonnucleoside reverse transcriptase inhibitor (NNRTI) class developed by Tibotec Inc. (Gilead's corporate partner) and has been approved on 5/20/11 as Edurant®(rilpivirine) tablets.

This resubmitted NDA application references the IND and NDA applications of the individual components, namely Gilead's IND 53,971, NDA 21-896 and NDA 21-500 for emtricitabine; Gilead's IND 52,849 and NDA 21-356 for tenofovir DF; Gilead's IND 67,671 and NDA 21-752 for emtricitabine/tenofovir DF, and cross-references Tibotec's IND 67,699 and NDA 202-022 for rilpivirine.

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BIOPHARMACEUTIC INFORMATION:

FTC/RPV/TDF tablets are an immediate-release solid oral dosage form (b) (4)

The Applicant claims that:

(b) (4)

Product's Formulation: Four drug product formulations were investigated during the drug product development. All 4 formulations were evaluated for *in vivo* bioequivalence to the reference drugs under fed conditions. Only formulation 3 (b) (4) showed bioequivalence to the reference drug products for all 3 components. Therefore, formulation 3 is the proposed commercial formulation and its composition is described below.

Ingredient	(b) (4) FTC/RPV/TDF Tablets (mg/tablet)
(b) (4)	
Rilpivirine HCl	27.5[a]
Microcrystalline Cellulose	(b) (4)
Lactose Monohydrate	
Povidone	
Polysorbate 20	
Croscarmellose Sodium	
Magnesium Stearate	
(b) (4)	
Emtricitabine	200.0
Tenofovir DF	300.0[b]
(b) (4)	
(b) (4)	(b) (4)
Film Coat (b) (4)	
(b) (4)	
(b) (4) Tablet Weight	1184.5

a Equivalent to 25.0 mg rilpivirine free base.

b Equivalent to 245 mg of tenofovir disoproxil

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Effect and rational of drug product formulation on drug release:

Laboratory data showed that the intrinsic dissolution rate of rilpivirine (b) (4)

(b) (4)

Dissolution Method

The proposed dissolution method for FTC/RPV/TDF fixed-dose combination tablets uses a paddle apparatus (USP Apparatus 2) operated at 75 rpm. The proposed dissolution medium consists of 1000 mL of 0.5% polysorbate 20 in 0.01N HCl (pH 2.0), at 37°C.

(b) (4)

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3) The access program tablets that have a different trade dress can be considered equivalent based on comparative release and stability dissolution data.

OVERALL CONCLUSION:

NDA 202-123 for Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed-Dose Combination Tablets (FTC/RPV/TDF) is recommended for approval.

There is a Phase IV Post-Marketing Commitment for NDA 202-123.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment	Office of New Drugs Quality Assessment

cc: Patrick Marroum, Ph.D.

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/s/

ELSBETH G CHIKHALE
07/15/2011

ANGELICA DORANTES
07/15/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202123	Submission Date: February 10, 2011
Brand Name	Complera®
Generic Name	Emtricitabine/rilpivirine/tenofovir disoproxil
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Sarah Robertson, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Gilead Sciences
Formulation; strength(s) to-be-marketed	Fixed dose combination tablet: emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil 300 mg
Proposed Indication	Treatment of HIV-1 infection in treatment naïve adult patients
Review Type	505 (b)(1) New Drug Application, priority review

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1 Executive Summary

This review summarizes the clinical pharmacology results for two trials evaluating fixed dose combination tablet formulations containing three antiretroviral medications for the treatment of HIV-1 infection. The three antiretroviral medications combined in the fixed dose combination tablet formulations are emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI), tenofovir, a nucleotide reverse transcriptase inhibitor, and rilpivirine, a non nucleoside reverse transcriptase inhibitor (NNRTI). All three medications are currently approved for marketing in the United States. The proposed dosage regimen and indication for the fixed dose combination tablet is once daily administration of 200 mg emtricitabine, 300 mg tenofovir, and 25 mg rilpivirine orally with a meal for the treatment of HIV-1 infection in treatment naïve adults.

Three trials were submitted as part of the New Drug Application. All three trials were conducted in healthy adults. There were no trials conducted with the fixed dose combination tablet formulations in HIV-1 infected subjects. One of the three trials (b) (4) US-264-101) was not reviewed because the fixed dose combination tablet formulations that were evaluated were not selected for potential marketing in the United States. The remaining two trials are discussed in this review. The first trial evaluated two fixed dose combination tablet formulations compared to the individual formulations of emtricitabine, tenofovir, and rilpivirine that are currently approved for marketing in the United States under fed conditions. The second trial evaluated the fixed dose combination tablet that was selected for potential marketing in the United States compared to the individual formulations of emtricitabine, tenofovir, and rilpivirine that are currently approved for marketing in the United States under fasted conditions. The applicant did not conduct a food effect trial for the fixed dose combination tablet that was selected for potential marketing in the United States.

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application.

1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this supplement.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

As outlined in the FDA Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations", the standard trial design for demonstrating bioequivalence of a new immediate release formulation is to compare the immediate release formulation to the reference formulation(s) with single dosing under fasting conditions. This comparison provides information on whether the two formulations being compared are bioequivalent (90% confidence intervals within 80%-125%). In contrast, for this NDA, the applicant conducted a trial (GS-US-264-103)

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evaluating the bioequivalence of two fixed dose combination formulations (test formulations 3 and 4) to the individual reference formulations under fed conditions (with a standardized meal). This type of trial evaluates bioequivalence under the conditions that the medication is administered to patients (e.g. with meals) but does not permit an evaluation regarding whether the formulations are bioequivalent because of the influence of food on drug exposure. Currently, based on the prescribing information for the individual formulations, rilpivirine should be administered with a meal; however tenofovir or emtricitabine may be administered without regard to food. The applicant also conducted a second trial (GS-US-264-108) evaluating the bioequivalence of test formulation 3 to the individual reference formulation under fasted conditions.

GS-US-264-103 was a Phase I, randomized, 3-way crossover clinical trial that enrolled healthy male and female subjects. Under fed conditions (a standardized breakfast with approximately 400 kcal and 13 grams of fat), two fixed dose combination tablet formulations (test formulation 3 and test formulation 4) were compared to the individual reference formulations of emtricitabine, tenofovir, and rilpivirine. The results of the statistical analyses for test formulation 3, the formulation that was selected for potential marketing in the United States, are presented in Table 1 through Table 3. The statistical analyses results for test formulation 4 are presented in section 3.1.

Table 1- GS-US-264-103 statistical analysis for a single 25 mg dose of rilpivirine administered under fed conditions as part of a fixed dose combination tablet (test formulation 3 for the test arm) compared to individual rilpivirine tablets (reference arm)

RPV PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC+RPV+TDF Reference (N=34)[a]		
AUC_{inf} (ng·h/mL)	3166.87	2738.56	115.64	108.71, 123.01
AUC_{last} (ng·h/mL)	2854.58	2466.92	115.71	109.13, 122.69
C_{max} (ng/mL)	109.57	94.56	115.87	108.21, 124.06

GLS = geometric least-squares

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet

FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

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Table 2- GS-US-264-103 statistical analysis for a single 200 mg dose of emtricitabine administered under fed conditions as part of a fixed dose combination tablet (test formulation 3 for the test arm) compared to individual emtricitabine capsules (reference arm)

FTC PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC+RPV+TDF Reference[a] (N=34)[a]		
AUC_{inf} (ng·h/mL)	9581.10	9594.63	99.86	97.67, 102.09
AUC_{last} (ng·h/mL)	9360.88	9366.29	99.94	97.77, 102.16
C_{max} (ng/mL)	1714.21	1625.23	105.47	100.46, 110.74

GLS = geometric least-squares
FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

Table 3- GS-US-264-103 statistical analysis for a single 300 mg dose of tenofovir administered under fed conditions as part of a fixed dose combination tablet (test formulation 3 for the test arm) compared to individual tenofovir tablets (reference arm)

TFV PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC+RPV+TDF Reference (N=34)[a]		
AUC_{inf} (ng·h/mL)	3264.17	3200.52	101.99	99.06, 105.00
AUC_{last} (ng·h/mL)	3053.10	2989.16	102.14	99.00, 105.38
C_{max} (ng/mL)	315.41	284.13	111.01	104.19, 118.28

GLS = geometric least-squares
FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

Based on the information presented in Tables 1 through 3, for the GS-US-264-103 trial, under fed conditions (a standardized breakfast with approximately 400 kcal and 13 grams of fat), the rilpivirine, tenofovir, and emtricitabine analytes were all bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ when comparing test formulation 3 to the individual reference formulations.

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For the GS-US-264-103 trial, a FDA Office of Scientific Investigations (OSI) inspection was requested for the bioanalytical laboratories [redacted] (b) (4) that analyzed rilpivirine, tenofovir, and emtricitabine plasma samples and the clinical trial site (SeaView Research). The inspections at [redacted] (b) (4) and SeaView Research did not result in the issuing of any 483 observations. Five 483 observations were issued based on the bioanalytical inspection conducted at [redacted] (b) (4)

1) A lack of sufficient long term stability data with emtricitabine, tenofovir and rilpivirine combined in the same matrix.
2) The removal of samples from the freezers was not documented in the freezer log books for the experiment that evaluated -20°C freeze thaw stability over three cycles for rilpivirine in the presence of emtricitabine and tenofovir.
3) Fresh calibration standards were not utilized in the autosampler stability experiment.
4) The laboratory notebooks did not document whether rilpivirine was protected from light either when rilpivirine was weighed or when subject samples from the GS-264-103 trial were processed.
5) For the validation study where stock solution stability was evaluated, audit trails were not available.

To address the first 483 observation, additional long term stability data was generated for rilpivirine in the presence of emtricitabine and tenofovir at-20°C and -70°C for up to 61 days and was acceptable. For the additional long term stability data, rilpivirine concentrations of 3 ng/mL and 1600 ng/mL were evaluated in the presence of emtricitabine and tenofovir concentrations of 2400 ng/mL and 600 ng/mL, respectively. For the second 483 observation, the OSI report states that while the information was not documented in the freezer log books, the sample processing sheets did contain the freezer numbers and the time that samples were removed from the freezers. In addition, [redacted] (b) (4) also updated both the freezer log template and the relevant Standard Operating Procedure. An additional autosampler stability experiment was conducted with fresh calibration standards and autosampler stability was demonstrated for up to 143 hours to address the third 483 observation. In response to the lack of documentation regarding whether subject samples from the GS-264-103 trial were processed under yellow light conditions, [redacted] (b) (4) stated that an increase in the [redacted] (b) (4) would have been observed with light exposure and this was monitored in the analytical runs for the GS-264-103 trial by including a sample containing a mix of rilpivirine and the [redacted] (b) (4). In the GS-264-103 trial, the [redacted] (b) (4) that was observed in the samples was less than 5 of rilpivirine, inferring that samples were analyzed under yellow light. OSI concurred with this assessment. Additionally, [redacted] (b) (4) also updated the relevant forms to document that rilpivirne is handled under yellow light. Lastly, to address the lack of available audit trials for the stock solution stability experiments that were conducted by [redacted] (b) (4) [redacted] (b) (4) conducted additional stock solution stability experiments at room temperature for 25 hours and at -20°C for up to 117 days that were acceptable.

GS-US-264-108 was a Phase I, randomized, 2-way crossover clinical trial that enrolled healthy male and female subjects. Under fasted conditions, a fixed dose combination tablet formulation (test formulation 3) was compared to the individual reference

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formulations of emtricitabine, tenofovir, and rilpivirine. The results of the statistical analyses are presented in Table 4 through Table 6.

Table 4-GS-US-264-108 statistical analysis for a single 25 mg dose of rilpivirine administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual rilpivirine tablets (reference arm)

RPV PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Interval
	FTC/RPV/TDF Test (N=15) [a]	FTC+RPV+TDF Reference (N=15) [a]		
AUC_{inf} (ng·h/mL)	2737.45	2183.88	125.35	(104.31, 150.63)
AUC_{last} (ng·h/mL)	2498.18	1941.59	128.67	(106.91, 154.85)
C_{max} (ng/mL)	77.66	62.14	124.97	(91.46, 170.75)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Table 5-GS-US-264-108 statistical analysis for a single 200 mg dose of emtricitabine administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual emtricitabine capsules (reference arm)

FTC PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Interval
	FTC/RPV/TDF Test (N=15) [a]	FTC+RPV+TDF Reference (N=15) [a]		
AUC_{inf} (ng·h/mL)	10,503.61	10,681.65	98.33	(95.13, 101.64)
AUC_{last} (ng·h/mL)	10,337.79	10494.01	98.51	(95.18, 101.95)
C_{max} (ng/mL)	2127.01	2249.21	94.57	(85.39, 104.73)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

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Table 6- GS-US-264-108 statistical analysis for a single 300 mg dose of tenofovir administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual tenofovir tablets (reference arm)

TFV PK Parameter	GLS Means		GLS Means Ratio (Test/Reference) (%)	90% Confidence Interval
	FTC/RPV/TDF Test (N=15) [a]	FTC+RPV+TDF Reference (N=15) [a]		
AUC_{inf} (ng·h/mL)	2441.55	2260.33	108.02	(92.63, 125.96)
AUC_{last} (ng·h/mL)	2249.34	2060.62	109.16	(91.37, 130.41)
C_{max} (ng/mL)	335.63	360.62	93.07	(79.06, 109.57)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

The fixed dose combination tablet formulation is not bioequivalent to the individual formulations of rilpivirine and tenofovir under fasted conditions. Based on the information presented in Tables 4 through 6, for the GS-US-264-108 trial, under fasted conditions, when comparing the fixed dose combination tablet (test formulation 3) to the individual reference formulations, only the emtricitabine component of the fixed dose combination tablet achieved bioequivalence for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. Under fasted conditions, the tenofovir and rilpivirine components of the fixed dose combination tablet (test formulation 3) were not bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ when comparing the fixed dose combination tablet to the individual reference formulations.

A food effect trial was not conducted for the fixed dose combination tablet that was selected for potential marketing in the United States. In response to an information request, the applicant submitted a cross trial comparison of the C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ pharmacokinetic data. The statistical analyses were conducted comparing the fed data from the GS-US-264-103 trial (test arm) to the fasted data from the GS-US-264-108 trial (reference arm). The results of the statistical analyses are presented in Table 7.

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Table 7-Cross trial statistical analysis for fixed dose combination tablet (test formulation 3) comparing fed conditions (test arm) to fasted conditions (reference arm)

	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	Test	Reference		
	FTC/RPV/TDF Under Fed Condition (N=34)[a]	FTC/RPV/TDF Under Fasted Condition (N=15)[b]		
Emtricitabine (FTC)				
AUC_{inf} (ng·h/mL)	9544.16	10500.54	90.89	84.36, 97.93
AUC_{last} (ng·h/mL)	9323.37	10335.49	90.21	83.65, 97.28
C_{max} (ng/mL)	1709.74	2135.38	80.07	71.35, 89.85
Rilpivirine (RPV)				
AUC_{inf} (ng·h/mL)	3147.83	2724.55	115.54	94.05, 141.93
AUC_{last} (ng·h/mL)	2842.46	2484.95	114.39	94.45, 138.54
C_{max} (ng/mL)	109.84	77.13	142.42	111.37, 182.12
Tenofovir (TFV)				
AUC_{inf} (ng·h/mL)	3255.80	2446.88	133.06	120.88, 146.46
AUC_{last} (ng·h/mL)	3045.53	2255.79	135.01	121.78, 149.68
C_{max} (ng/mL)	314.12	337.08	93.19	81.37, 106.72

a Subjects 3008 and 3026 did not have PK parameter data due to premature study drug discontinuation and were excluded from analysis.

b Subject 4007 did not have PK parameter data due to premature study drug discontinuation and was excluded from analysis.

Based on the cross trial comparison, the following conclusions were derived regarding the potential effect of food with the fixed dose combination tablet:

- Food may result in a clinically significant change in rilpivirine exposure. The rilpivirine C_{max}, $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-inf})}$ increased by 42%, 14%, and 16%, respectively, when comparing fed [a standardized meal with approximately 400 kcal and 13 grams of fat] to fasted conditions. The effect of food appears to be attenuated when compared to the observed food effect with the individual rilpivirine tablets. For the individual rilpivirine tablets, under fasted condition, the rilpivirine exposure was decreased by approximately 40% when compared to a standardized meal (533 kcal) meal or a high fat, high calorie meal (928 kcal).
- Food is not anticipated to result in a clinically significant change in tenofovir and emtricitabine exposure. The C_{max} for emtricitabine and tenofovir was decreased by 20% and 7%, respectively, the $AUC_{(0\text{-last})}$ for emtricitabine was decreased by 10% and increased for tenofovir by 35%, and the $AUC_{(0\text{-inf})}$ for emtricitabine was decreased by 9% and increased for tenofovir by 33% when comparing fed to fasted conditions**.** With the exception of the decrease in tenofovir C_{max}, these changes in exposures with a standardized meal (approximately 400 kcal and 13 grams of fat) were consistent

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with the changes described in the prescribing information with high fat meals for the individual emtricitabine and tenofovir formulations that can currently be administered with or without food.

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3 Appendices

3.1 Individual Trial Reviews

3.1.1 GS-US-264-103 trial

1. Title

Bioequivalence Study of Two, Fixed-dose, Combination Tablet Formulations Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the Concurrent Administration of the Individual Components

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at SeaView Research, Inc. Miami, FL 33126 from February 12, 2010 to April 12, 2010.

3. Objectives

The primary objective of the trial were to evaluate the bioequivalence under fed conditions of two different fixed dose combination tablets (each formulation containing 200 mg emtricitabine, 300 mg tenofovir, and 25 mg rilpivirine) compared to the individual formulations of 200 mg emtricitabine, 300 mg tenofovir, and 25 mg rilpivirine.

4. Trial Design

GS-US-264-103 was a Phase I, randomized, 3-way crossover clinical trial that enrolled healthy male and female subjects between 18 and 45 years old. The washout period was at least 14 days after Periods 1 and 2. There were six different sequences for the trial. The trial design is displayed in Figure 1 and the treatment sequences are displayed in Table 1.

Figure 1- GS-US-264-103 trial design

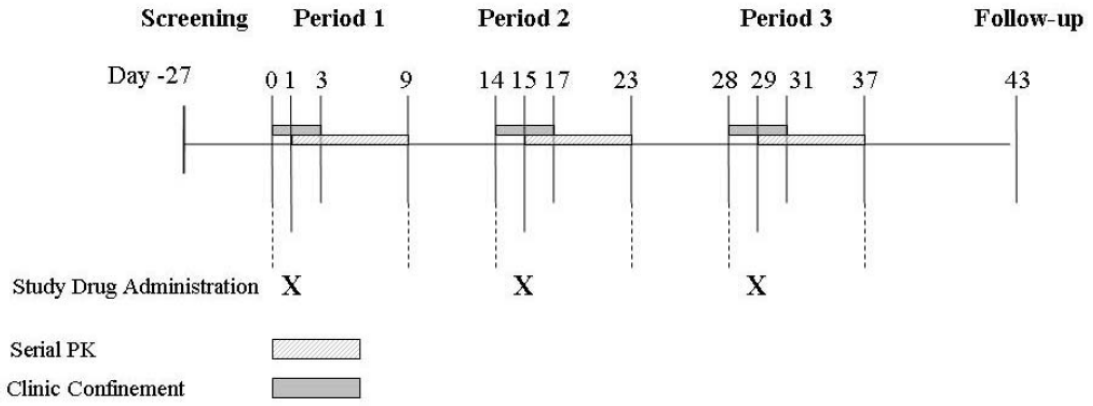

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Table 1-Treatment sequences for the GS-US-264-103 trial

Sequence	Day 1	Day 15	Day 29
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Treatment A (reference): a single dose of FTC 1 × 200-mg capsule, RPV 1 × 25-mg tablet, and TDF 1 × 300-mg tablet administered together

Treatment B: (test formulation 3): a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

Treatment C: (test formulation 4): a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen, vitamins, acetaminophen, and hormonal contraceptives was permitted during the trial. Use of topical hydrocortisone cream or A and D ointment to treat skin irritation from ECG leads was also permitted. All other prescription, nonprescription, herbal medications, and antacids were to be discontinued within 28 days of initial dosing for the trial.

Other restrictions during the trial included the use of food or beverages containing alcohol, nicotine or products containing nicotine, grapefruit, grapefruit juice, and Seville orange juice. The use of tea, coffee, chocolate, and other food and beverages containing caffeine and other methylxanthines was not permitted on dosing days.

6. Dosage and Administration

On Days 1, 15, and 29, after fasting overnight for at least 8 hours, trial medications were administered within five minutes of a standardized breakfast. Water was not permitted from one hour before to two hours after trial medication was administered with the exception of 240 milliliters of water that was administered with the trial medication. The standardized breakfast that was administered on dosing days was to contain approximately 400 kcal and 13 grams of fat.

7. Rationale for Doses Used in the Trial

A single 25 mg rilpivirine dose was evaluated in the trial for the fixed dose combination tablets and the individual rilpivirine tablets. The recommended rilpivirine dosage regimen in the current rilpivirine U.S. prescribing information for HIV-1 infected treatment naïve adults is 25 mg once daily with a meal.

A single 200 mg emtricitabine dose was evaluated in the trial for the fixed dose combination tablets and the individual emtricitabine capsules. The recommended dosage

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regimen in the current emtricitabine U.S. prescribing information for HIV-1 infected adults is 200 mg once daily without regard to food.

A single 300 mg tenofovir dose was evaluated in the trial for the fixed dose combination tablets and the individual tenofovir tablets. The recommended dosage regimen in the current tenofovir U.S. prescribing information for HIV-1 infected adults is 300 mg once daily without regard to food.

8. Drugs Used in the Trial

Information regarding the emtricitabine, tenofovir, and rilpivirine formulations that were administered in the trial is displayed in Table 2. The applicant confirmed that the emtricitabine and tenofovir commercial drug products are the US commercially marketed products.

Table 2-Information on the emtricitabine, tenofovir, and rilpivirine formulations administered in the GS-US-264-103 trial

	Fixed-Dose Combination Tablet Formulation 3	Fixed-Dose Combination Tablet Formulation 4	Emtricitabine Emtriva® Capsules[a]	Tenofovir DF Viread® Tablets[a]	Rilpivirine Tablets
Strength	FTC 200 mg RPV 25 mg[b] TDF 300 mg	FTC 200 mg RPV 25 mg[b] TDF 300 mg	200 mg	300 mg	25 mg[b]
Lot Size	(b) (4)				
Lot No.	BY1001B1	BY1002B1	56766AF21	A117181A	9CL1F
Mfg. Date	December 2009	December 2009	September 2007	March 2009	March 2009
Expiration Date	December 2011	December 2011	September 2010	March 2013	March 2011
Manufacturer/ Supplier	(b) (4)				
Country of Purchase	Not applicable	Not applicable	Not applicable	Not applicable	USA
Site of Release in Europe	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

FTC = emtricitabine, GSI = Gilead Sciences, Inc., Mfg = manufacturing, RPV = rilpivirine, TDF = tenofovir disoproxil fumarate

a Commercial drug product

b RPV as 27.5 mg of the hydrochloride salt

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9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Emtricitabine, tenofovir, and rilpivirine blood samples were obtained starting on Days 1, 15, and 29 in Periods 1, 2, and 3, respectively, at predose and up to 192 hours postdose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a partially validated LC/MS/MS method in sodium heparin anticoagulated plasma by (b) (4). The blood samples for analysis of rilpivirine were collected in tubes containing lithium heparin as an anticoagulant. A validation experiment was conducted evaluating rilpivirine quality control samples containing sodium heparin as an anticoagulant compared to rilpivirine quality control samples containing lithium heparin as an anticoagulant. The experiment demonstrated that there were no accuracy or precision issues with using either anticoagulant with rilpivirine as an analyte. According to the applicant, the partially validated method is the same method validated by Tibotec under BA1071. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the GS-US-264-103 trial, precision and accuracy were evaluated using plasma QC samples at four concentration levels: 3 ng/mL, 50 ng/mL, 200 ng/mL, and 1600 ng/mL. The 200 ng/mL concentration level was not evaluated during method validation and was added based on the prediction that the reported concentrations would be between 50 ng/mL and 1600 ng/mL for the trial. The corresponding rilpivirine inter-run accuracy values were 2.3% for 3 ng/mL, -1.6% for 50 ng/mL, -2% for 200 ng/mL, and -1.2% for 1600 ng/mL. The rilpivirine inter-run precision values were 6.6% for 3 ng/mL, 5% for 50 ng/mL, 4.9% for 200 ng/mL, and 6.1% for 1600 ng/mL. For the GS-US-264-103 trial, the rilpivirine samples were stored at -70°C at the clinical trial site, and at the bioanalytical laboratory, the rilpivirine samples were stored at -20°C except for the samples from the first two periods. The samples from the first two periods were initially stored at -70°C. While rilpivirine long term stability data of 1528 days at -20°C in plasma matrix was submitted, additional long term stability data is needed for rilpivirine in the presence of emtricitabine and tenofovir to cover the duration of long term rilpivirine stability data necessary for the GS-US-264-103 trial (approximately 60 days). There is no long term stability data currently available for rilpivirine at -70°C. However, long term stability data for rilpivirine in the presence of emtricitabine and tenofovir at both -20°C and -70°C was generated and additional data was submitted (see below).

The method and bioanalysis of emtricitabine and tenofovir is acceptable. Plasma samples were analyzed for emtricitabine and tenofovir concentrations using a validated LC/MS/MS method in K_2EDTA by (b) (4) The lower limit of quantification for emtricitabine was 5 ng/mL and the upper limit of quantification was 3000 ng/mL. There were no precision or accuracy issues identified for emtricitabine based on the

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bioanalytical report. For the GS-US-264-103 trial, precision and accuracy were evaluated using plasma QC samples at four concentration levels: 15 ng/mL, 150 ng/mL, 600 ng/mL and 2400 ng/mL. The corresponding emtricitabine inter-run accuracy values were 0.7% for 15 ng/mL, 2.3% for 150 ng/mL, 2.1% for 600 ng/mL, and -0.3% for 2400 ng/mL. The emtricitabine inter-run precision values were 4.2% for 15 ng/mL, 4% for 150 ng/mL, 3.7% for 600 ng/mL, and 3.1% for 2400 ng/mL. For the GS-US-264-103 trial, the emtricitabine and tenofovir samples were stored at -70°C both at the clinical trial site and the bioanalytical laboratory. Long term emtricitabine stability data of 190 days in plasma matrix at -20°C and -70°C and 181 days (6 months) at -70°C for emtricitabine in the presence of tenofovir and rilpivirine covered the duration of long term emtricitabine stability data necessary for the GS-US-264-103 trial. The lower limit of quantification for tenofovir was 5 ng/mL and the upper limit of quantification was 3000 ng/mL. There were no precision or accuracy issues identified for tenofovir based on the bioanalytical report. For the GS-US-264-103 trial, precision and accuracy were evaluated using plasma QC samples at four concentration levels: 15 ng/mL, 150 ng/mL, 600 ng/mL and 2400 ng/mL. The corresponding tenofovir inter-run accuracy values were -0.1% for 15 ng/mL, 3.4% for 150 ng/mL, 4.9% for 600 ng/mL, and 1.1% for 2400 ng/mL. The tenofovir inter-run precision values were 5.3% for 15 ng/mL, 4.2% for 150 ng/mL, 4.4% for 600 ng/mL and 3.6% for 2400 ng/mL. Long term tenofovir stability data of 190 days in plasma matrix at -20°C and -70°C and 92 days at -70°C for tenofovir in the presence of emtricitabine and rilpivirine covered the duration of long term tenofovir stability data necessary for the GS-US-264-103 trial.

Additional selectivity, freeze thaw and long term stability method validation experiments for emtricitabine and tenofovir in the presence of rilpivirine were conducted by (b) (4) The selected concentration of 300 ng/mL of rilpivirine that was evaluated for the emtricitabine and tenofovir assay was acceptable. There were no issues identified with the additional selectivity, freeze thaw and long term stability method validation experiments for emtricitabine and tenofovir in the presence of 300 ng/mL of rilpivirine with the exception of the tenofovir long term stability data. For the freeze thaw and long term stability method validation experiments, emtricitabine and tenofovir concentrations of 15 ng/mL and 2400 ng/mL, respectively, were evaluated in the presence of 300 ng/mL of rilpivirine. At six months at -70°C, for 2400 ng/mL of tenofovir, the change in the mean tenofovir concentration was greater than 15% when compared to Day 0 tenofovir concentrations but the change in the mean tenofovir concentration was less than 15% when compared to the nominal concentration of 2400 ng/mL.

Additional freeze thaw and long term stability method validation experiments for rilpivirine in the presence of emtricitabine and tenofovir were conducted by (b) (4) (b) (4) A selectivity experiment for rilpivirine in the presence of emtricitabine and tenofovir was not initially conducted. For the freeze thaw and long term stability method validation experiments, rilpivirine concentrations of 3 ng/mL and 1600 ng/mL were evaluated in the presence of the selected emtricitabine and tenofovir concentrations of 500 ng/mL and 200 ng/mL, respectively. According to the applicant, the emtricitabine and tenofovir concentrations were selected based on the emtricitabine and tenofovir C_{max} values from the published literature. However, the clinical pharmacology reviewer

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determined that the selected emtricitabine and tenofovir values were not representative of the observed C_{max} values for the GS-US-264-103 and GS-US-264-108 trials and recommended the evaluation of rilpivirine in the presence of emtricitabine and tenofovir concentrations of 2400 ng/mL and 600 ng/mL, respectively. The applicant agreed to conduct the additional selectivity, freeze thaw, and long term stability experiments for rilpivirine in the presence of emtricitabine and tenofovir. There were no issues identified with the additional selectivity experiment or the additional freeze thaw and long term stability method validation experiments that were conducted at -20°C and -70°C with emtricitabine concentrations of 500 ng/mL or 2400 ng/mL and tenofovir concentrations of 200 ng/mL or 600 ng/mL.

The FDA Office of Scientific Investigations (OSI) was requested to conduct an inspection of the two bioanalytical laboratories that analyzed rilpivirine, emtricitabine and tenofovir plasma samples and the clinical trial site for the GS-US-264-103 trial. Five 483 observations were issued for (b) (4). The details of the 483 observations that were issued by OSI and a discussion of the explanations or follow up actions from (b) (4) for each of the 483 observations is provided in section 1.3. There were no 483 observations issued for either the (b) (4) bioanalytical laboratory or the clinical trial site (Sea View Research).

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. Plasma concentration values that were below the lower limit of quantification (5 ng/mL for emtricitabine and tenofovir and 1 ng/mL for rilpivirine) prior to the first quantifiable concentration were converted to zero and all other plasma concentration values that were below the lower limit of quantification were labeled as "missing". The plasma pharmacokinetic parameters were derived by the applicant using WinNonlin version 5.2. The linear up/log down trapezoidal method was used along with actual sampling times, when feasible, in calculating the pharmacokinetic parameters. The bioequivalence assessment was conducted using SAS.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, emtricitabine, and tenofovir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), median, and the minimum and maximum values.

Statistical analysis for rilpivirine, emtricitabine, and tenofovir involved comparing the natural log transformed C_{max}, $AUC_{0\text{-inf})}$, and $AUC_{0\text{-inf})}$ parameters for the two fixed dose combination formulations (test arm) to the individual formulations (reference arm). Using a mixed effects model, geometric least squares means were calculated and 90% confidence intervals were derived. For the 90% confidence interval, the predefined range (lower and upper limit) for achieving bioequivalence in exposure for C_{max}, $AUC_{(0\text{-last})}$,

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and $AUC_{(0\text{-inf})}$ was 80% to 125%.

10. Results

10.1 Subject Demographics and Disposition

Table 3-GS-US-264-103 subject demographics

Characteristic	N=36
Sex, n (%)	
Male	15 (41.7%)
Female	21 (58.3%)
Age (years)	
Mean (SD)	33 (7.0)
Median	32
Min, Max	19, 45
Race, (n, %)	
White	27 (75.0%)
Black	9 (25.0%)
Ethnicity	
Hispanic/Latino	32 (88.9%)
Non-Hispanic/Latino	4 (11.1%)
Height at Screening	
Mean (SD)	167.9 (9.68)
Median	166.0
Min, Max	150.0, 190.0
Weight at Screening	
Mean (SD)	71.9 (10.97)
Median	70.7
Min, Max	50.8, 92.7
Body-Mass Index[a] at Screening	
Mean (SD)	25.4 (2.48)
Median	25.8
Min, Max	19.6, 29.0
Estimated Creatinine Clearance (mL/minute)[b]	
Mean (SD)	128.0 (17.91)
Median	129.0
Min, Max	91.4, 157.4

a Body-mass index = weight (kg) / height $(cm)^2 \times 10{,}000$

b Estimated creatinine clearance = (140 − age [y]) × weight [kg]) / serum creatinine [mg/dL] × 72) for male subjects; equation × 0.85 for female subjects

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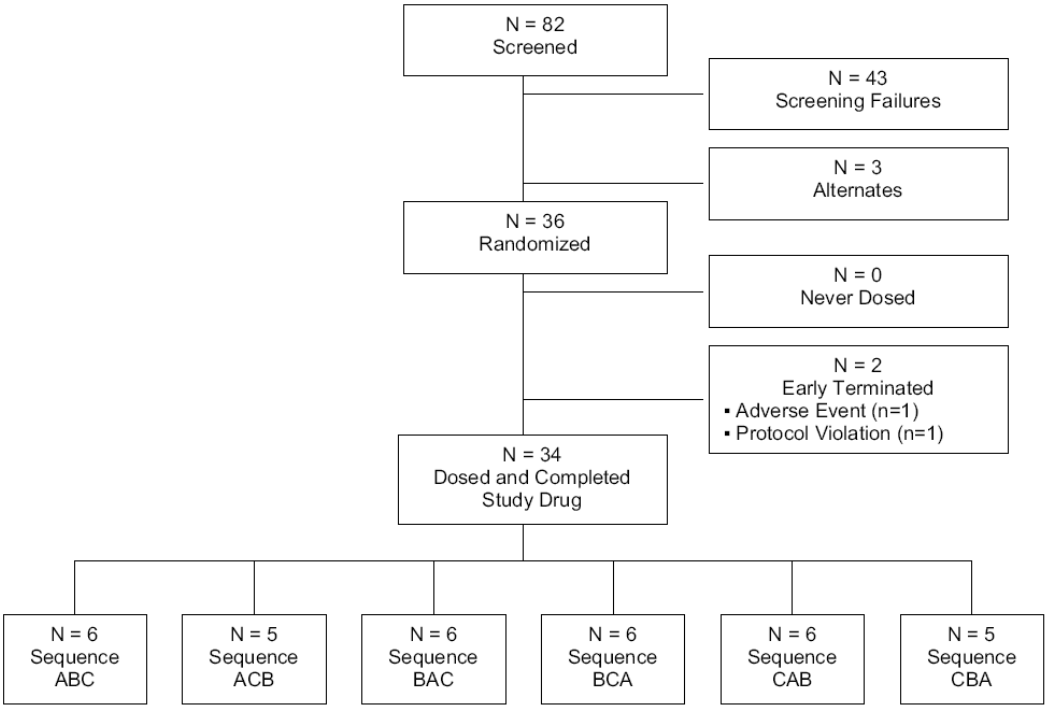
Figure 2-GS-US-264-103 subject disposition



Subjects were randomized equally into one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA).
Treatment A (reference): a single dose of FTC 1 × 200-mg capsule, RPV 1 × 25-mg tablet (as 27.5 mg of the hydrochloride salt), and TDF 1 × 300-mg tablet
Treatment B (test formulation 3): a single dose of FDC tablet (FTC 200 mg/RPV 25 mg [as 27.5 mg of the hydrochloride salt]/TDF 300 mg)
Treatment C (test formulation 4): a single dose of FDC tablet (FTC 200 mg/RPV 25 mg [as 27.5 mg of the hydrochloride salt]/TDF 300 mg)

10.2 Prior and Concomitant Medications

Two subjects administered concurrent medications during the trial. Both subjects administered ibuprofen, loratadine, and loratadine in combination with pseudoephedrine. The medications were administered starting on April 3, 2010 or later. The concomitant medications are not expected to impact the reported plasma concentration data from the GS-US-264-103 trial because the last dose was administered on March 20, 2010.

10.3 Pharmacokinetic and Statistical Analysis

For subjects receiving rilpivirine in either the second or third period, there were seven subjects receiving the reference formulation, and eight and six subjects receiving test formulation 3 and 4, respectively, with quantifiable predose rilpivirine concentrations. However, these concentrations were 5% or less of the subject's C_{max} for the period, and no adjustments were necessary for the pharmacokinetic analyses. There were no subjects with quantifiable predose rilpivirine concentrations in the first period. All subjects had emtricitabine and tenofovir predose concentrations that were less than the lower limit of quantification (LLOQ) for all three periods.

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10.3.1 Applicant Pharmacokinetic and Statistical Analysis

Rilpivirine (RPV)

Table 4-Pharmacokinetic parameters for a single 25 mg dose of rilpivirine administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4) and as individual rilpivirine tablets

RPV PK Parameter	FTC+RPV+TDF Reference (N=34) [a]	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC/RPV/TDF Test Formulation 4 (N=34)[a]
C_{max} (ng/mL) Mean (%CV)	99.8 (30.5)	115.5 (29.6)	122.7 (32.4)
T_{max} (h) Median (Q1, Q3)	4.50 (4.00, 4.50)	4.50 (4.00, 4.50)	4.50 (3.50, 4.50)
C_{last} (ng/mL) Mean (%CV)	3.4 (72.8)	4.1 (72.9)	4.1 (75.9)
T_{last} (h) Median (Q1, Q3)	192.00 (192.00, 192.40)	192.00 (192.00, 193.00)	192.00 (192.00, 193.00)
AUC_{last} (ng·h/mL) Mean (%CV)	2597.2 (32.5)	3014.4 (34.5)	3037.4 (32.4)
AUC_{inf} (ng·h/mL) Mean (%CV)	2923.3 (38.6)	3389.3 (39.4)	3422.7 (38.1)
AUC_{exp} (%) Mean (%CV)	9.6 (69.3)	9.5 (68.5)	9.6 (70.1)
$T_{½}$ (h) Median (Q1, Q3)	53.12 (40.17, 65.46)	54.19 (39.03, 62.85)	54.67 (37.55, 65.73)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet

FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

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Table 5-Statistical analysis for a single 25 mg dose of rilpivirine administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4 for the test arms) compared to individual rilpivirine tablets (reference arm)

RPV PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC+RPV+TDF Reference (N=34)[a]		
AUC_{inf} (ng·h/mL)	3166.87	2738.56	115.64	108.71, 123.01
AUC_{last} (ng·h/mL)	2854.58	2466.92	115.71	109.13, 122.69
C_{max} (ng/mL)	109.57	94.56	115.87	108.21, 124.06
RPV PK Parameter	**FTC/RPV/TDF Test Formulation 4 (N=34)[a]**	**FTC+RPV+TDF Reference (N=34)[a]**	**GLS Means Ratio (Test/Reference) (%)**	**90% Confidence Intervals**
AUC_{inf} (ng·h/mL)	3211.23	2738.56	117.26	110.24, 124.73
AUC_{last} (ng·h/mL)	2888.99	2466.92	117.11	110.45, 124.17
C_{max} (ng/mL)	115.02	94.56	121.63	113.59, 130.23

GLS = geometric least-squares

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet

FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

Statistical analyses were conducted for rilpivirine administered as 25 mg single doses of rilpivirine under fed conditions comparing a fixed dose combination tablet (either test formulation 3 or 4) to individual rilpivirine tablets. For test formulation 3, the 90% confidence interval for rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%. For test formulation 4, the 90% confidence interval for rilpivirine $AUC_{(0\text{-inf})}$ and $AUC_{(0\text{-last})}$, were within 80%-125% but the 90% confidence interval for rilpivirine C_{max} was not within 80%-125%.

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Emtricitabine (FTC)

Table 6-Pharmacokinetic parameters for a single 200 mg dose of emtricitabine administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4) and as individual emtricitabine capsules

FTC PK Parameter	FTC+RPV+TDF Reference (N=34)[a]	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC/RPV/TDF Test Formulation 4 (N=34)[a]
C_{max} (ng/mL) Mean (%CV)	1652.8 (21.9)	1753.9 (23.6)	1809.5 (28.6)
T_{max} (h) Median (Q1, Q3)	2.00 (2.00, 2.50)	2.50 (2.00, 3.00)	2.50 (2.00, 3.50)
C_{last} (ng/mL) Mean (%CV)	8.2 (29.1)	8.6 (35.0)	8.3 (33.1)
T_{last} (h) Median (Q1, Q3)	72.00 (48.00, 72.00)	72.00 (48.00, 72.00)	72.00 (48.00, 72.00)
AUC_{last} (ng·h/mL) Mean (%CV)	9417.5 (13.9)	9416.5 (14.3)	9494.1 (14.3)
AUC_{inf} (ng·h/mL) Mean (%CV)	9644.5 (13.6)	9636.3 (14.1)	9705.2 (13.9)
AUC_{exp} (%) Mean (%CV)	2.4 (49.7)	2.3 (45.4)	2.2 (52.6)
$T_{½}$ (h) Median (Q1, Q3)	19.03 (14.36, 20.78)	18.30 (14.30, 20.16)	16.38 (13.24, 20.97)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet

FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

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Table 7-Statistical analysis for a single 200 mg dose of emtricitabine administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4 for the test arms) compared to individual emtricitabine capsules (reference arm)

FTC PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC+RPV+TDF Reference[a] (N=34)[a]		
AUC_{inf} (ng·h/mL)	9581.10	9594.63	99.86	97.67, 102.09
AUC_{last} (ng·h/mL)	9360.88	9366.29	99.94	97.77, 102.16
C_{max} (ng/mL)	1714.21	1625.23	105.47	100.46, 110.74
FTC PK Parameter	**FTC/RPV/TDF Test Formulation 4 (N=34)[a]**	**FTC+RPV+TDF Reference[a] (N=34)[a]**	**GLS Means Ratio (Test/Reference) (%)**	**90% Confidence Intervals**
AUC_{inf} (ng·h/mL)	9646.25	9594.63	100.54	98.34, 102.79
AUC_{last} (ng·h/mL)	9432.71	9366.29	100.71	98.52, 102.94
C_{max} (ng/mL)	1753.57	1625.23	107.90	102.77, 113.28

GLS = geometric least-squares

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet

FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

Statistical analyses were conducted for emtricitabine administered as 200 mg single doses of emtricitabine under fed conditions comparing a fixed dose combination tablet (either test formulation 3 or 4) to individual emtricitabine capsules. For both test formulation 3 and test formulation 4, the 90% confidence interval for emtricitabine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

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Tenofovir (TDF)

Table 8-Pharmacokinetic parameters for a single 300 mg dose of tenofovir administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4 for the test arms) and as individual tenofovir tablets (reference arm)

TFV PK Parameter	FTC+RPV+TDF Reference (N=34)[a]	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC/RPV/TDF Test Formulation 4 (N=34)[a]
C_{max} (ng/mL) Mean (%CV)	291.1 (26.4)	324.7 (26.0)	334.1 (26.4)
T_{max} (h) Median (Q1, Q3)	1.50 (1.00, 2.00)	2.00 (2.00, 2.50)	2.25 (1.50, 2.50)
C_{last} (ng/mL) Mean (%CV)	8.1 (29.4)	7.9 (26.3)	8.3 (34.0)
T_{last} (h) Median (Q1, Q3)	72.00 (48.00, 72.00)	72.00 (72.00, 72.00)	72.00 (72.00, 72.00)
AUC_{last} (ng·h/mL) Mean (%CV)	3040.3 (21.3)	3108.2 (21.1)	3177.7 (21.3)
AUC_{inf} (ng·h/mL) Mean (%CV)	3246.8 (19.7)	3313.6 (19.7)	3392.7 (19.6)
AUC_{exp} (%) Mean (%CV)	6.6 (32.3)	6.4 (32.7)	6.6 (39.7)
$T_{½}$ (h) Median (Q1, Q3)	18.14 (16.82, 19.41)	18.12 (16.60, 19.45)	18.56 (16.48, 20.46)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

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Table 9-Statistical analysis for a single 300 mg dose of tenofovir administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4 for the test arms) compared to individual tenofovir tablets (reference arm)

TFV PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Intervals
	FTC/RPV/TDF Test Formulation 3 (N=34)[a]	FTC+RPV+TDF Reference (N=34)[a]		
AUC_{inf} (ng·h/mL)	3264.17	3200.52	101.99	99.06, 105.00
AUC_{last} (ng·h/mL)	3053.10	2989.16	102.14	99.00, 105.38
C_{max} (ng/mL)	315.41	284.13	111.01	104.19, 118.28
TFV PK Parameter	**FTC/RPV/TDF Test Formulation 4 (N=34)[a]**	**FTC+RPV+TDF Reference[a] (N=34)**	**GLS Means Ratio (Test/Reference) (%)**	**90% Confidence Intervals**
AUC_{inf} (ng·h/mL)	3333.11	3200.52	104.14	101.15, 107.22
AUC_{last} (ng·h/mL)	3110.38	2989.16	104.06	100.86, 107.35
C_{max} (ng/mL)	323.41	284.13	113.83	106.83, 121.28

GLS = geometric least-squares

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet

FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

a Subjects 3648-3008 and 3648-3026 did not have PK data for a treatment pair of interest and were excluded.

Statistical analyses were conducted for tenofovir administered as 300 mg single doses of tenofovir under fed conditions comparing a fixed dose combination tablet (either test formulation 3 or 4) to individual emtricitabine capsules. For both test formulation 3 and test formulation 4, the 90% confidence interval for tenofovir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

10.3.2 FDA Pharmacokinetic and Statistical Analysis

The clinical pharmacology reviewer conducted an independent analysis of the plasma concentration data for rilpivirine, emtricitabine and tenofovir that was submitted by Gilead. Rilpivirine, emtricitabine and tenofovir pharmacokinetic parameters and the bioequivalence analysis was derived using WinNonlin version 5.2. The linear up/log down trapezoidal method was used along with nominal sampling times in calculating the pharmacokinetic parameters. Plasma concentration values that were below the lower limit of quantification (5 ng/mL for emtricitabine and tenofovir and 1 ng/mL for rilpivirine) were converted to zero before the T_{max} occurrence and "missing" after the T_{max} occurrence. The elimination phase for individual subject profiles was selected by the WinNonlin program. In Tables 10 through 18 below, data is presented for the mean rilpivirine, emtricitabine and tenofovir T_{max}, C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ values that were derived and the analysis comparing the two fixed dose combination formulations to the individual rilpivirine, emtricitabine and tenofovir formulations.

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Rilpivirine (RPV)

Table 10-Pharmacokinetic parameters for a single 25 mg dose of rilpivirine administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4) and as individual rilpivirine tablets

Rilpivirine (RPV) PK parameter	RPV+FTC+TDF (Individual reference formulations) N=35	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV/FTC/TDF (fixed dose combination test formulation 4) N=35
C_{max} (ng/mL) Mean (SD)	99.6 (30)	115.5 (34.2)	123.5 (39.4)
T_{max} (hr) Median	4.5	4.5	4.5
$AUC_{(0\text{-last})}$ (ng*hr/mL) Mean (SD)	2617.7 (841.8)	3012.3 (1037.7)	3063.1 (982.7)
$AUC_{(0\text{-inf})}$ (ng*hr/mL) Mean (SD)	2938.6 (1115.7)	3396.1 (1339.9)	3522.1 (1463.3)

SD=standard deviation, hr=hour

Table 11-Statistical analysis for a single 25 mg dose of rilpivirine administered under fed conditions as part of a fixed dose combination tablet (test formulation 3 for the test arm) compared to individual rilpivirine tablets (reference arm)

Rilpivirine (RPV) PK parameter	Rilpivirine geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV+FTC+TDF (Individual reference formulations) N=34		
C_{max} (ng/mL)	109.6	94.6	115.9	108.2%-124.1%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	2852.8	2466	115.7	109.1%-122.7%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	3172.7	2724.8	116.4	109.3%-124.1%

(Analysis excludes data from subjects 8 and 26)

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Table 12-Statistical analysis for a single 25 mg dose of rilpivirine administered under fed conditions as part of a fixed dose combination tablet (test formulation 4 for the test arm) compared to individual rilpivirine tablets (reference arm)

Rilpivirine (RPV) PK parameter	Rilpivirine geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV+FTC+TDF (Individual reference formulations) N=34		
C_{max} (ng/mL)	115	94.6	121.6	113.6%-130.2%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	2887.2	2466	117.1	110.4%-124.1%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	3233	2724.8	118.7	111.4%-126.4%

(Analysis excludes data from subjects 8 and 26)

The FDA statistical analyses evaluated rilpivirine administered as 25 mg single doses of rilpivirine under fed conditions with a fixed dose combination tablet (either test formulation 3 or 4) compared to individual rilpivirine tablets. The results of the analyses were similar to the results reported by the applicant for test formulation 3 but different for test formulation 4. For test formulation 3, the 90% confidence interval for rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%. For test formulation 4, the 90% confidence interval for rilpivirine $AUC_{(0\text{-last})}$ was within 80%-125% but the 90% confidence interval for rilpivirine C_{max} and $AUC_{(0\text{-inf})}$ were not within 80%-125%. In contrast, for test formulation 4, the applicant reported that the 90% confidence interval for rilpivirine $AUC_{(0\text{-inf})}$ was within 80%-125%. However, the difference in the upper limit of the 90% confidence interval for $AUC_{(0\text{-inf})}$ when comparing the results reported by the applicant and the FDA analysis results is minor. The conclusions for the trial regarding rilpivirine exposure for test formulation 4 when compared to the individual rilpivirine tablets are unchanged because in both the FDA analysis and the applicant's analysis, the 90% confidence interval was not within 80%-125% for all three rilpivirine parameters [C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$].

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Emtricitabine (FTC)

Table 13-Pharmacokinetic parameters for a single 200 mg dose of emtricitabine administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4) and as individual emtricitabine capsules

Emtricitabine (FTC) PK parameter	RPV+FTC+TDF (Individual reference formulations) N=35	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV/FTC/TDF (fixed dose combination test formulation 4) N=35
C_{max} (ng/mL) Mean (SD)	1647.2 (358.6)	1753.9 (413.7)	1803.4 (511.5)
T_{max} (hr) Median	2	2.5	2.5
$AUC_{(0\text{-last})}$ (ng*hr/mL) Mean (SD)	9397.9 (1295.6)	9415.2 (1348)	9509.4 (1339.7)
$AUC_{(0\text{-inf})}$ (ng*hr/mL) Mean (SD)	9639 (1291.6)	9646 (1368.6)	9732.4 (1331.9)

SD=standard deviation, hr=hour

Table 14-Statistical analysis for a single 200 mg dose of emtricitabine administered under fed conditions as part of a fixed dose combination tablet (test formulation 3 for the test arm) compared to individual emtricitabine capsules (reference arm)

Emtricitabine (FTC) PK parameter	Emtricitabine geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV+FTC+TDF (Individual reference formulations) N=34		
C_{max} (ng/mL)	1714.2	1625.2	105.5	100.5%-110.7%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	9359.6	9364.2	100	97.8%-102.2%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	9589.1	9607.1	99.8	97.5%-102.1%

(Analysis excludes data from subjects 8 and 26)

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Table 15-Statistical analysis for a single 200 mg dose of emtricitabine administered under fed conditions as part of a fixed dose combination tablet (test formulation 4 for the test arm) compared to individual emtricitabine capsules (reference arm)

Emtricitabine (FTC) PK parameter	Emtricitabine geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV+FTC+TDF (Individual reference formulations) N=34		
C_{max} (ng/mL)	1753.6	1625.2	107.9	102.8%-113.3%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	9431.9	9364.2	100.7	98.5%-103%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	9657.8	9607.1	100.5	98.2%-102.9%

(Analysis excludes data from subjects 8 and 26)

The FDA statistical analyses evaluated emtricitabine administered as 200 mg single doses of emtricitabine under fed conditions with a fixed dose combination tablet (either test formulation 3 or 4) compared to individual emtricitabine capsules. The results of the analyses were similar to the results reported by the applicant. For both test formulation 3 and test formulation 4, the 90% confidence interval for emtricitabine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

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Tenofovir (TDF)

Table 16-Pharmacokinetic parameters for a single 300 mg dose of tenofovir administered under fed conditions as part of a fixed dose combination tablet (test formulations 3 and 4) and as individual tenofovir tablets

Tenofovir (TDF) PK parameter	RPV+FTC+TDF (Individual reference formulations) N=35	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV/FTC/TDF (fixed dose combination test formulation 4) N=35
C_{max} (ng/mL) Mean (SD)	291.6 (75.7)	324.7 (84.6)	337.1 (88.7)
T_{max} (hr) Median	1.5	2	2.5
$AUC_{(0\text{-last})}$ (ng*hr/mL) Mean (SD)	3065.6 (654.9)	3108 (655)	3214.5 (701.7)
$AUC_{(0\text{-inf})}$ (ng*hr/mL) Mean (SD)	3265 (651.2)	3304.2 (653.9)	3420.9 (693.2)

SD=standard deviation, hr=hour

Table 17-Statistical analysis for a single 300 mg dose of tenofovir administered under fed conditions as part of a fixed dose combination tablet (test formulation 3 for the test arm) compared to individual tenofovir tablets (reference arm)

Tenofovir (TDF) PK parameter	Tenofovir geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV+FTC+TDF (Individual reference formulations) N=34		
C_{max} (ng/mL)	315.4	284.1	111	104.2%- 118.3%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	3052.9	2988.8	102.1	99%- 105.4%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	3253.9	3191.3	102	99%- 105%

(Analysis excludes data from subjects 8 and 26)

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Table 18-Statistical analysis for a single 300 mg dose of tenofovir administered under fed conditions as part of a fixed dose combination tablet (test formulation 4 for the test arm) compared to individual tenofovir tablets (reference arm)

Tenofovir (TDF) PK parameter	Tenofovir geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination test formulation 3) N=34	RPV+FTC+TDF (Individual reference formulations) N=34		
C_{max} (ng/mL)	323.4	284.1	113.8	106.8%-121.3%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	3110.2	2988.8	104.1	100.9%-107.4%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	3323.3	3191.3	104.1	101.1%-107.3%

(Analysis excludes data from subjects 8 and 26)

The FDA statistical analyses evaluated tenofovir administered as 300 mg single doses of tenofovir under fed conditions with a fixed dose combination tablet (either test formulation 3 or 4) compared to individual tenofovir tablets. The results of the analyses were similar to the results reported by the applicant. For both test formulation 3 and test formulation 4, the 90% confidence interval for tenofovir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. Testicular pain was the only adverse event reported in more than one or more subjects with the two events occurring with the reference treatment.

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Table 19-Summary of treatment emergent adverse events

Adverse Event Category, n (%)	FTC+RPV+TDF Reference (N=35)	FTC/RPV/TDF Test Formulation 3 (N=34)	FTC/RPV/TDF Test Formulation 4 (N=35)
Any treatment-emergent AE	3 (8.6%)	4 (11.8%)	4 (11.4%)
Study drug-related treatment-emergent AE	2 (5.7%)	2 (5.9%)	2 (5.7%)
Grade 3 or 4 treatment-emergent AE	0	0	0
Treatment-emergent AE that led to permanent discontinuation of study drug	0	0	1 (2.9%)
Any treatment-emergent SAE	0	0	0
Death	0	0	0

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test formulation 3 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
FTC/RPV/TDF FDC test formulation 4 = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

11. Discussion and Conclusions

Based on the results from the GS-US-264-103 trial, the following conclusions can be made based on the applicant's analysis:

- Under fed conditions, when rilpivirine was administered as 25 mg single doses of rilpivirine with a fixed dose combination tablet (either test formulation 3 or 4) compared to individual rilpivirine tablets, only test formulation 3 was bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. The C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ ratios were all increased by 16%. The 90% confidence interval for all three parameters was within 80% to 125%. For test formulation 4, the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ ratios were increased by 17%, and the C_{max} ratio was increased by 22%. The 90% confidence interval for C_{max} was not within 80% to 125% (both AUC parameters were within 80% to 125%).
- Under fed conditions, when emtricitabine was administered as 200 mg single doses of emtricitabine with a fixed dose combination tablet (either test formulation 3 or 4) compared to individual emtricitabine capsules, both test formulation 3 and test formulation 4 were bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. The 90% confidence interval for all three parameters was within 80% to 125% for both formulations. For test formulation 3, the C_{max} ratio was increased by 5%, and the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ ratios were decreased by less than 1%. For test formulation 4, the C_{max} ratio was increased by 8%, and the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ ratios were both increased by 1%.

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- When tenofovir was administered as 300 mg single doses of tenofovir under fed conditions with a fixed dose combination tablet (either test formulation 3 or 4) compared to individual tenofovir tablets, both test formulation 3 and test formulation 4 were bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. The 90% confidence interval for all three parameters was within 80% to 125%. For test formulation 3, the C_{max} ratio was increased by 11%, and the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ ratios were both increased by 2%. For test formulation 4, the C_{max} ratio was increased by 14%, and the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ ratios were both increased by 4%.

An independent analysis by the clinical pharmacology reviewer confirmed the applicant's results and conclusions, with the exception of a minor difference in the upper limit of the 90% confidence interval for rilpivirine $AUC_{(0\text{-inf})}$ that was reported for test formulation 4. The difference is analysis results do not alter the trial's conclusions regarding rilpivirine exposure for test formulation 4 when compared to the individual rilpivirine tablets.

Both the applicant's analysis and the FDA analysis support the following conclusions when comparing the fixed dose combination tablet to the individual reference formulations under fasted conditions: a) for test formulation 3, all 3 components (rilpivirine, emtricitabine, and tenofovir) of the fixed dose combination tablet were bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$, and b) for test formulation 4, only the emtricitabine and tenofovir components of the fixed dose combination tablet were bioequivalent for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$.

Based on the trial results, the applicant selected test formulation 3 as the proposed commercial rilpivirine, emtricitabine and tenofovir fixed dose combination tablet for marketing in the United States.

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3.1.2 GS-US-264-108 trial

1. Title

Relative Bioavailability Study of a Fixed-dose, Combination Tablet Formulation Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the Concurrent Administration of the Individual Components

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at SeaView Research, Inc. Miami, FL 33126 from May 10, 2010 to June 11, 2010.

3. Objectives

The primary objective of the trial were to evaluate the bioequivalence under fasted conditions of a fixed dose combination tablet formulation (each formulation containing 200 mg emtricitabine, 300 mg tenofovir, and 25 mg rilpivirine) compared to the individual formulations of 200 mg emtricitabine, 300 mg tenofovir, and 25 mg rilpivirine.

4. Trial Design

GS-US-264-108 was a Phase I, randomized, 2-way crossover clinical trial that enrolled healthy male and female subjects between 18 and 45 years old. The washout period was at least 14 days after Period 1. There were two different sequences for the trial. The trial design is displayed in Figure 1 and the treatment sequences are displayed in Table 1.

Figure 1-GS-US-264-108 trial design

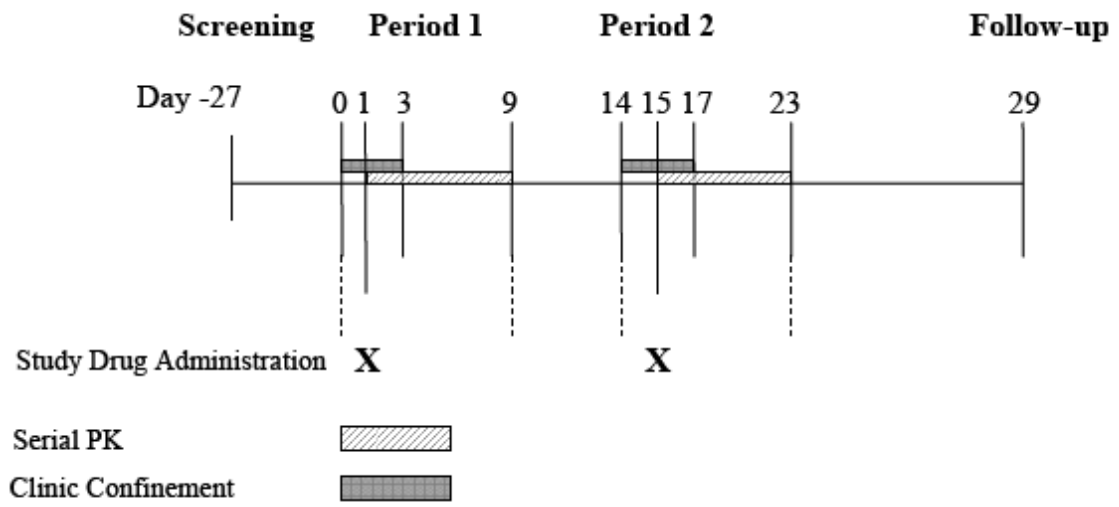

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Table 1-Treatment sequences for the GS-US-264-108 trial

Sequence	Day 1	Day 15
1	A	B
2	B	A

Treatment A: (reference): single doses of FTC 1 × 200-mg strength capsule, RPV 1 × 25-mg strength tablet, and TDF 1 × 300-mg strength tablet administered together

Treatment B: (test): a single dose of FDC tablet (FTC 200 mg, RPV 25 mg, and TDF 300 mg)

5. Exclusion and Inclusion Criteria/Other Restrictions and Exceptions

Use of ibuprofen, vitamins, acetaminophen, and hormonal contraceptives was permitted during the trial. Use of topical hydrocortisone cream or A and D ointment to treat skin irritation from ECG leads was also permitted. All other prescription, nonprescription, herbal medications, and antacids were to be discontinued within 28 days of initial dosing for the trial.

Other restrictions during the trial included the use of food or beverages containing alcohol, nicotine or products containing nicotine, grapefruit, grapefruit juice, and Seville orange juice. The use of tea, coffee, chocolate, and other food and beverages containing caffeine and other methylxanthines was not permitted on dosing days.

6. Dosage and Administration

On Days 1 and 15, after fasting overnight for at least 8 hours, trial medications were administered with 240 mL of water. Water was not permitted from one hour before to two hours after trial medication was administered with the exception of 240 milliliters of water that was administered with the trial medication.

7. Rationale for Doses Used in the Trial

A single 25 mg rilpivirine dose was evaluated in the trial for the fixed dose combination tablets and the individual rilpivirine tablets. The recommended rilpivirine dosage regimen in the current rilpivirine U.S. prescribing information for HIV-1 infected treatment naive adults is 25 mg once daily with a meal.

A single 200 mg emtricitabine dose was evaluated in the trial for the fixed dose combination tablets and the individual emtricitabine capsules. The recommended dosage regimen in the current emtricitabine U.S. prescribing information for HIV-1 infected adults is 200 mg once daily without regard to food.

A single 300 mg tenofovir dose was evaluated in the trial for the fixed dose combination tablets and the individual tenofovir tablets. The recommended dosage regimen in the current tenofovir U.S. prescribing information for HIV-1 infected adults is 300 mg once daily without regard to food.

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8. Drugs Used in the Trial

Information regarding the emtricitabine, tenofovir, and rilpivirine formulations that were administered in the trial is displayed in Table 1. The applicant confirmed that the emtricitabine and tenofovir commercial drug products are the US commercially marketed products. Based on the lot number displayed in Table 2 for the fixed dose combination tablet formulation, the formulation that was administered in the GS-US-264-108 trial was test formulation 3 in the GS-US-264-103 trial.

Table 2-Information on the emtricitabine, tenofovir, and rilpivirine formulations administered in the GS-US-264-108 trial

	FTC/RPV/TDF FDC Tablet	Emtricitabine Emtriva® Capsules[a]	Tenofovir DF Viread® Tablets[a]	Rilpivirine Tablets
Strength	FTC 200 mg RPV 25 mg[b] TDF 300 mg	200 mg	300 mg	25 mg[b]
Lot Size	(b) (4)			
Lot No.	BY1001B1	56766AF21	A117181A	9CL1F
Mfg. Date	December 2009	September 2007	March 2009	March 2009
Expiration Date	December 2011	September 2010	March 2013	March 2011
Manufacturer/ Supplier	(b) (4)			
Country of Purchase	Not applicable	Not applicable	Not applicable	USA
Site of Release in Europe	Not applicable	Not applicable	Not applicable	Not applicable

FTC = emtricitabine, GSI = Gilead Sciences, Inc., Mfg = manufacturing, RPV = rilpivirine, TDF = tenofovir disoproxil fumarate

a Commercial drug product

b RPV as 27.5 mg of the hydrochloride salt

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9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Emtricitabine, tenofovir, and rilpivirine blood samples were obtained starting on Days 1 and 15 in Periods 1 and 2, respectively, at predose and up to 192 hours postdose.

Bioanalysis

The method and bioanalysis of rilpivirine are acceptable. Rilpivirine plasma samples were analyzed using a partially validated LC/MS/MS method in sodium heparin anticoagulated plasma by (b) (4) The blood samples for analysis of rilpivirine were collected in tubes containing lithium heparin as an anticoagulant. A validation experiment was conducted evaluating rilpivirine quality control samples containing sodium heparin as an anticoagulant compared to rilpivirine quality control samples containing lithium heparin as an anticoagulant. The experiment demonstrated that there were no accuracy or precision issues with using either anticoagulant with rilpivirine as an analyte. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the GS-US-264-108 trial, precision and accuracy were evaluated using plasma QC samples at four concentration levels: 3 ng/mL, 50 ng/mL, and 1600 ng/mL. The corresponding rilpivirine inter-run accuracy values were 0.3% for 3 ng/mL, -2% for 50 ng/mL, and 1.3% for 1600 ng/mL. The rilpivirine inter-run precision values were 6.4% for 3 ng/mL, 3.5% for 50 ng/mL, and 4.6% for 1600 ng/mL. For the GS-US-264-108 trial, the rilpivirine samples were stored at -70°C at the clinical trial site, and at the bioanalytical laboratory, the rilpivirine samples were stored at -20°C. While rilpivirine long term stability data of 1528 days at -20°C in plasma matrix was submitted, additional long term stability data is needed for rilpivirine in the presence of emtricitabine and tenofovir to cover the duration of long term rilpivirine stability data necessary for the GS-US-264-108 trial (approximately 30 days). There is no long term stability data currently available for rilpivirine at -70°C. However, long term stability data for rilpivirine in the presence of emtricitabine and tenofovir at both -20°C and -70°C was generated and additional data was submitted (see below).

The method and bioanalysis of emtricitabine and tenofovir is acceptable. Plasma samples were analyzed for emtricitabine and tenofovir concentrations using a validated LC/MS/MS method in K_2EDTA by (b) (4) The lower limit of quantification for emtricitabine was 5 ng/mL and the upper limit of quantification was 3000 ng/mL. There were no precision or accuracy issues identified for emtricitabine based on the bioanalytical report. For the GS-US-264-108 trial, precision and accuracy were evaluated using plasma QC samples at four concentration levels: 15 ng/mL, 150 ng/mL, 600 ng/mL and 2400 ng/mL. The corresponding emtricitabine inter-run accuracy values were 0% for 15 ng/mL, 0.3% for 150 ng/mL, -1.8% for 600 ng/mL, and 0.1% for 2400 ng/mL. The emtricitabine inter-run precision values were 5.2% for 15 ng/mL, 3.3% for

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150 ng/mL, 3.7% for 600 ng/mL, and 3.0% for 2400 ng/mL. For the GS-US-264-108 trial, the emtricitabine and tenofovir samples were stored at -70°C both at the clinical trial site and the bioanalytical laboratory. Long term emtricitabine stability data of 190 days in plasma matrix at -20°C and -70°C and 181 days (6 months) at -70°C for emtricitabine in the presence of tenofovir and rilpivirine covered the duration of long term emtricitabine stability data necessary for the GS-US-264-108 trial. The lower limit of quantification for tenofovir was 5 ng/mL and the upper limit of quantification was 3000 ng/mL. There were no precision or accuracy issues identified for tenofovir based on the bioanalytical report. For the GS-US-264-108 trial, precision and accuracy were evaluated using plasma QC samples at four concentration levels: 15 ng/mL, 150 ng/mL, 600 ng/mL and 2400 ng/mL. The corresponding tenofovir inter-run accuracy values were -5.1% for 15 ng/mL, 1.6% for 150 ng/mL, -5.5% for 600 ng/mL, and 0.9% for 2400 ng/mL. The tenofovir inter-run precision values were 6% for 15 ng/mL, 3.5% for 150 ng/mL, 3.4% for 600 ng/mL and 3.2% for 2400 ng/mL. Long term tenofovir stability data of 190 days in plasma matrix at -20°C and -70°C and 92 days at -70°C for tenofovir in the presence of emtricitabine and rilpivirine covered the duration of long term tenofovir stability data necessary for the GS-US-264-108 trial.

Additional selectivity, freeze thaw and long term stability method validation experiments for emtricitabine and tenofovir in the presence of rilpivirine were conducted by (b) (4) The selected concentration of 300 ng/mL of rilpivirine that was evaluated for the emtricitabine and tenofovir assay was acceptable. There were no issues identified with the additional selectivity, freeze thaw and long term stability method validation experiments for emtricitabine and tenofovir in the presence of 300 ng/mL of rilpivirine with the exception of the tenofovir long term stability data. For the freeze thaw and long term stability method validation experiments, emtricitabine and tenofovir concentrations of 15 ng/mL and 2400 ng/mL, respectively, were evaluated in the presence of 300 ng/mL of rilpivirine. At six months at -70°C, for 2400 ng/mL of tenofovir, the change in the mean tenofovir concentration was greater than 15% when compared to Day 0 tenofovir concentrations but the change in the mean tenofovir concentration was less than 15% when compared to the nominal concentration of 2400 ng/mL.

Additional freeze thaw and long term stability method validation experiments for rilpivirine in the presence of emtricitabine and tenofovir were conducted by (b) (4) (b) (4) A selectivity experiment for rilpivirine in the presence of emtricitabine and tenofovir was not initially conducted. For the freeze thaw and long term stability method validation experiments, rilpivirine concentrations of 3 ng/mL and 1600 ng/mL were evaluated in the presence of the selected emtricitabine and tenofovir concentrations of 500 ng/mL and 200 ng/mL, respectively. According to the applicant, the emtricitabine and tenofovir concentrations were selected based on the emtricitabine and tenofovir C_{max} values from the published literature. However, the clinical pharmacology reviewer determined that the selected emtricitabine and tenofovir values were not representative of the observed C_{max} values for the GS-US-264-103 and GS-US-264-108 trials and recommended the evaluation of rilpivirine in the presence of emtricitabine and tenofovir concentrations of 2400 ng/mL and 600 ng/mL, respectively. The applicant agreed to conduct the additional selectivity, freeze thaw, and long term stability experiments for

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rilpivirine in the presence of emtricitabine and tenofovir. There were no issues identified with the additional selectivity experiment or the additional freeze thaw and long term stability method validation experiments that were conducted at -20°C and -70°C with emtricitabine concentrations of 500 ng/mL or 2400 ng/mL and tenofovir concentrations of 200 ng/mL or 600 ng/mL.

There was no FDA inspection requested for the two bioanalytical laboratories that analyzed rilpivirine, emtricitabine and tenofovir plasma samples or the clinical trial site for the GS-US-264-108 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed to calculate plasma pharmacokinetic parameters, including C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. Plasma concentration values that were below the lower limit of quantification (5 ng/mL for emtricitabine and tenofovir and 1 ng/mL for rilpivirine) prior to the first quantifiable concentration were converted to zero and all other plasma concentration values that were below the lower limit of quantification were labeled as "missing". The plasma pharmacokinetic parameters were derived by the applicant using WinNonlin version 6.1. The linear up/log down trapezoidal method was used along with actual sampling times, when feasible, in calculating the pharmacokinetic parameters. The bioequivalence assessment was conducted using SAS.

Statistical Analysis

Descriptive statistics were calculated for rilpivirine, emtricitabine, and tenofovir plasma concentrations and pharmacokinetic parameters, including the number of subjects (n), mean, standard deviation, the coefficient of variation (CV%), median, and the minimum and maximum values.

Statistical analysis for rilpivirine, emtricitabine, and tenofovir involved comparing the natural log transformed C_{max}, $AUC_{0\text{-inf})}$, and $AUC_{0\text{-inf})}$ parameters for the fixed dose combination formulation (test arm) to the individual formulations (reference arm). Using a mixed effects model, geometric least squares means were calculated and 90% confidence intervals were derived. For the 90% confidence interval, there was no predefined range (lower and upper limit) specified by the applicant for achieving bioequivalence in exposure for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$. For the purposes of this review, 90% confidence interval limits of 80%-125% will be used as the criteria for achieving bioequivalence in exposure.

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10. Results

10.1 Subject Demographics and Disposition

Table 3-GS-US-264-108 subject demographics

Characteristic	Safety Analysis Set N=16
Sex, n (%)	
Male	8 (50.0%)
Female	8 (50.0%)
Age (years)	
Mean (SD)	32 (6.1)
Median	34
Min, Max	20, 43
Race, n (%)	
White	9 (56.3%)
Black	7 (43.8%)
Ethnicity, n (%)	
Hispanic/Latino	13 (81.3%)
Non-Hispanic/Latino	3 (18.8%)
Height at screening (cm)	
Mean (SD)	167.0 (8.85)
Median	166
Min, Max	153.5, 182.0
Weight at screening (kg)	
Mean (SD)	70.6 (8.57)
Median	70.0
Min, Max	56.9, 86.7
Body mass index[a] at screening (kg/m^2)	
Mean (SD)	25.3 (1.92)
Median	25.1
Min, Max	20.7, 28.1
Estimated creatinine clearance (mL/min)[b]	
Mean (SD)	127.1 (16.07)
Median	125.4
Min, Max	98.2, 167.5

a Body mass index = weight (kg) / height (cm)^2

b Creatinine clearance estimated by Cockcroft-Gault = (140 − age [y]) × weight [kg]) / serum creatinine [mg/dL] × 72) for male subjects; equation × 0.85 for female subjects

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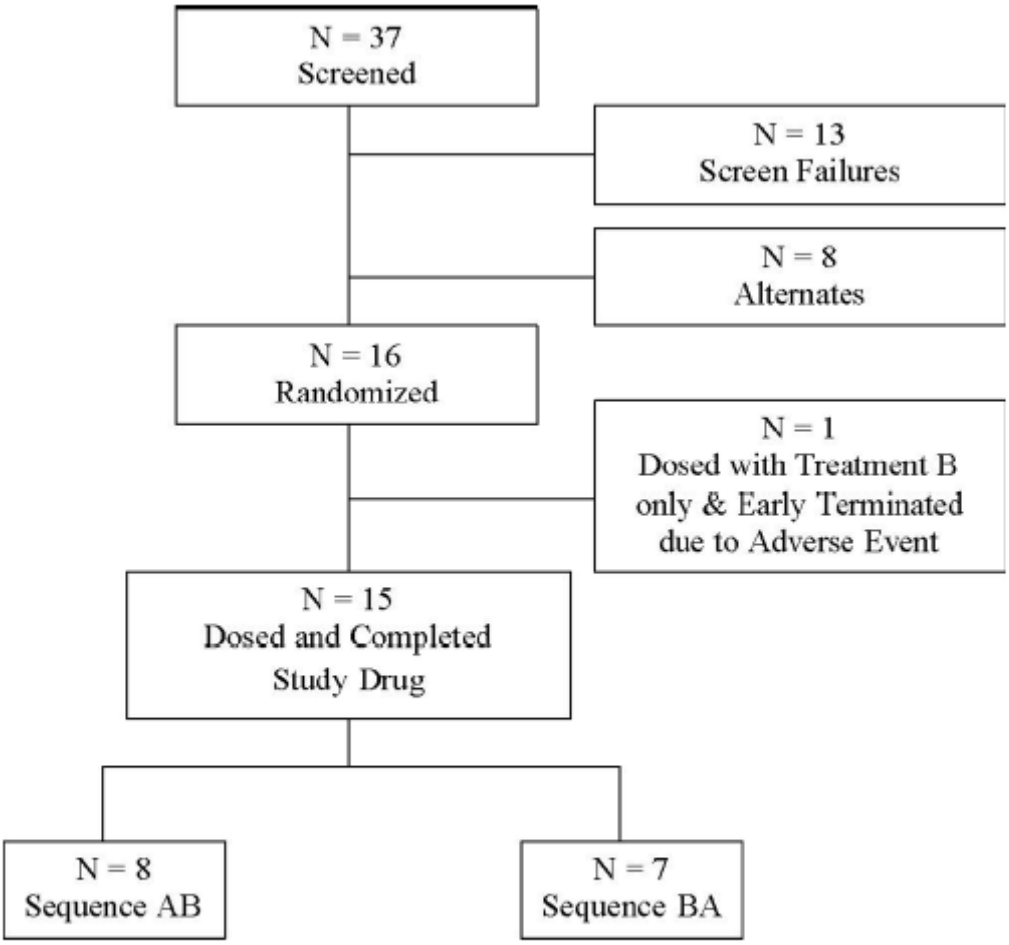
Figure 2-GS-US-264-108 subject disposition



Sequence AB: treatment A (reference) on Day 1 followed by treatment B (test) on Day 15
Sequence BA: treatment B (test) on Day 1 followed by treatment A (reference) on Day 15

10.2 Prior and Concomitant Medications

One subject administered concurrent medications during the trial. The subject administered acetaminophen and loratadine. The use of these two medications is not expected to impact the reported plasma concentration data from the GS-US-264-108 trial based on the current information regarding the ability of acetaminophen or loratadine to affect the exposure of other medications.

10.3 Pharmacokinetic and Statistical Analysis

One subject receiving the rilpivirine reference formulation in the second period had a quantifiable predose rilpivirine concentration. However, the predose concentration was 5% or less of the subject's C_{max} for the period, and no adjustments were necessary for the pharmacokinetic analyses. All subjects had emtricitabine and tenofovir predose concentrations that were less than the lower limit of quantification (LLOQ) for both

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periods.

10.3.1 Applicant Pharmacokinetic and Statistical Analysis

Rilpivirine (RPV)

Table 4-Pharmacokinetic parameters for a single 25 mg dose of rilpivirine administered under fasted conditions as part of a fixed dose combination tablet and as individual rilpivirine tablets

RPV PK Parameter	FTC + RPV + TDF Reference (N=15)[a]	FTC/RPV/TDF Test (N=15)[a]
C_{max} (ng/mL) Mean (%CV)	64.9 (27.2)	91.8 (53.4)
T_{max} (h) Median (Q1, Q3)	3.50 (3.00, 4.50)	3.50 (3.00, 4.00)
C_{last} (ng/mL) Mean (%CV)	2.6 (38.8)	3.0 (55.4)
T_{last} (h) Median (Q1, Q3)	192.0 (192.0, 192.0)	192.0 (192.0, 192.0)
AUC_{last} (ng·h/mL) Mean (%CV)	2031.6 (28.6)	2668.4 (37.4)
AUC_{inf} (ng·h/mL) Mean (%CV)	2277.4 (27.5)	2932.3 (39.1)
AUC_{exp} (%) Mean (%CV)	10.7 (57.6)	8.7 (50.6)
$T_{½}$ (h) Median (Q1, Q3)	56.09 (49.53, 72.25)	54.78 (41.46, 64.75)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Table 5-Statistical analysis for a single 25 mg dose of rilpivirine administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual rilpivirine tablets (reference arm)

RPV PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Interval
	FTC/RPV/TDF Test (N=15) [a]	FTC+RPV+TDF Reference (N=15) [a]		
AUC_{inf} (ng·h/mL)	2737.45	2183.88	125.35	(104.31, 150.63)
AUC_{last} (ng·h/mL)	2498.18	1941.59	128.67	(106.91, 154.85)
C_{max} (ng/mL)	77.66	62.14	124.97	(91.46, 170.75)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Statistical analyses were conducted for rilpivirine administered as 25 mg single doses of rilpivirine under fasted conditions comparing fixed dose combination tablets to individual rilpivirine tablets. For the fixed dose combination tablets, the 90% confidence interval for rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were not within 80%-125%.

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Emtricitabine (FTC)

Table 6-Pharmacokinetic parameters for a single 200 mg dose of emtricitabine administered under fasted conditions as part of a fixed dose combination tablet and as individual emtricitabine capsules

FTC PK Parameter	FTC + RPV + TDF Reference (N=15)[a]	FTC/RPV/TDF Test (N=15)[a]
C_{max} (ng/mL) Mean (%CV)	2343.1 (27.7)	2180.2 (21.8)
T_{max} (h) Median (Q1, Q3)	1.00 (1.00, 1.50)	1.50 (1.00, 2.50)
C_{last} (ng/mL) Mean (%CV)	9.0 (42.0)	7.7 (33.9)
T_{last} (h) Median (Q1, Q3)	48.00 (48.00, 72.00)	72.00 (48.00, 72.00)
AUC_{last} (ng·h/mL) Mean (%CV)	10,632.5 (16.3)	10,445.4 (15.4)
AUC_{inf} (ng·h/mL) Mean (%CV)	10,820.1 (16.2)	10,611.4 (15.4)
AUC_{exp} (%) Mean (%CV)	1.7 (47.2)	1.6 (31.2)
$T_{½}$ (h) Median (Q1, Q3)	14.84 (9.73, 16.85)	15.80 (10.61, 17.98)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Table 7-Statistical analysis for a single 200 mg dose of emtricitabine administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual emtricitabine capsules (reference arm)

FTC PK Parameter	GLS Mean		GLS Means Ratio (Test/Reference) (%)	90% Confidence Interval
	FTC/RPV/TDF Test (N=15)[a]	FTC+RPV+TDF Reference (N=15)[a]		
AUC_{inf} (ng·h/mL)	10,503.61	10,681.65	98.33	(95.13, 101.64)
AUC_{last} (ng·h/mL)	10,337.79	10494.01	98.51	(95.18, 101.95)
C_{max} (ng/mL)	2127.01	2249.21	94.57	(85.39, 104.73)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Statistical analyses were conducted for emtricitabine administered as 200 mg single doses of emtricitabine under fasted conditions comparing fixed dose combination tablets to individual emtricitabine capsules. For the fixed dose combination tablets, the 90% confidence interval for emtricitabine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

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Tenofovir (TDF)

Table 8-Pharmacokinetic parameters for a single 300 mg dose of tenofovir administered under fasted conditions as part of a fixed dose combination tablet and as individual tenofovir tablets

TFV PK Parameter	FTC + RPV + TDF Reference (N=15)[a]	FTC/RPV/TDF Test (N=15)[a]
C_{max} (ng/mL) Mean (%CV)	380.6 (31.2)	347.5 (25.9)
T_{max} (h) Median (Q1, Q3)	0.75 (0.75, 0.75)	0.75 (0.75, 1.50)
C_{last} (ng/mL) Mean (%CV)	8.1 (25.5)	8.5 (19.5)
T_{last} (h) Median (Q1, Q3)	48.00 (48.00, 72.00)	48.00 (48.00, 72.00)
AUC_{last} (ng·h/mL) Mean (%CV)	2218.3 (34.1)	2295.5 (21.0)
AUC_{inf} (ng·h/mL) Mean (%CV)	2399.6 (31.3)	2484.5 (19.4)
AUC_{exp} (%) Mean (%CV)	8.8 (55.9)	7.8 (25.1)
$T_{½}$ (h) Median (Q1, Q3)	16.08 (13.73, 17.07)	14.43 (13.31, 17.99)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Table 9-Statistical analysis for a single 300 mg dose of tenofovir administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual tenofovir tablets (reference arm)

TFV PK Parameter	GLS Means		GLS Means Ratio (Test/Reference) (%)	90% Confidence Interval
	FTC/RPV/TDF Test (N=15)[a]	FTC+RPV+TDF Reference (N=15)[a]		
AUC_{inf} (ng·h/mL)	2441.55	2260.33	108.02	(92.63, 125.96)
AUC_{last} (ng·h/mL)	2249.34	2060.62	109.16	(91.37, 130.41)
C_{max} (ng/mL)	335.63	360.62	93.07	(79.06, 109.57)

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)
a Subject 2848-4007 did not have PK data for a treatment pair of interest and was excluded from summaries.

Statistical analyses were conducted for tenofovir administered as 300 mg single doses of tenofovir under fasted conditions comparing fixed dose combination tablets to individual tenofovir tablets. For the fixed dose combination tablets, the 90% confidence interval for tenofovir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were not within 80%-125%.

10.3.2 FDA Pharmacokinetic and Statistical Analysis

The clinical pharmacology reviewer conducted an independent analysis of the plasma concentration data for rilpivirine, emtricitabine and tenofovir that was submitted by

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Gilead. Rilpivirine, emtricitabine and tenofovir pharmacokinetic parameters and the bioequivalence analysis was derived using WinNonlin version 5.2. The linear up/log down trapezoidal method was used along with nominal sampling times in calculating the pharmacokinetic parameters. Plasma concentration values that were below the lower limit of quantification (5 ng/mL for emtricitabine and tenofovir and 1 ng/mL for rilpivirine) were converted to zero before the T_{max} occurrence and "missing" after the T_{max} occurrence. The elimination phase for individual subject profiles was selected by the WinNonlin program. In Tables 10 through 15 below, data is presented for the mean rilpivirine, emtricitabine and tenofovir T_{max}, C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ values that were derived and the analysis comparing the fixed dose combination tablet to the individual rilpivirine, emtricitabine and tenofovir formulations.

Rilpivirine (RPV)

Table 10-Pharmacokinetic parameters for a single 25 mg dose of rilpivirine administered under fasted conditions as part of a fixed dose combination tablet and as individual rilpivirine tablets

Rilpivirine (RPV) PK parameter	RPV+FTC+TDF (Individual reference formulations) N=15	RPV/FTC/TDF (fixed dose combination tablet) N=16
C_{max} (ng/mL) Mean (SD)	64.9 (17.6)	90.6 (47.6)
T_{max} (hr) Median	3.5	3.5
$AUC_{(0\text{-last})}$ (ng*hr/mL) Mean (SD)	2031.6 (580.3)	2712.4 (979.9)
$AUC_{(0\text{-inf})}$ (ng*hr/mL) Mean (SD)	2244.9 (640.7)	2984.8 (1111.8)

SD=standard deviation, hr=hour

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Table 11-Statistical analysis for a single 25 mg dose of rilpivirine administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual rilpivirine tablets (reference arm)

Rilpivirine (RPV) PK parameter	Rilpivirine geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination tablet) N=15	RPV+FTC+TDF (Individual reference formulations) N=15		
C_{max} (ng/mL)	77.7	62.1	125	91.5%-170.8%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	2498.1	1941.6	128.7	106.9%-154.9%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	2717.1	2145.2	126.7	105.6%-152%

(Analysis excludes data from subject 7)

The FDA statistical analyses evaluated rilpivirine administered as 25 mg single doses of rilpivirine under fasted conditions with fixed dose combination tablets compared to individual rilpivirine tablets. The results of the analyses were similar to the results reported by the applicant. For the fixed dose combination tablets, the 90% confidence interval for rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were not within 80%-125%.

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Emtricitabine (FTC)

Table 12-Pharmacokinetic parameters for a single 200 mg dose of emtricitabine administered under fasted conditions as part of a fixed dose combination tablet and as individual emtricitabine capsules (reference)

Emtricitabine (FTC) PK parameter	RPV+FTC+TDF (Individual reference formulations) N=15	RPV/FTC/TDF (fixed dose combination tablet) N=16
C_{max} (ng/mL) Mean (SD)	2343.1 (649.2)	2158.3 (467.8)
T_{max} (hr) Median	1	1.5
$AUC_{(0\text{-last})}$ (ng*hr/mL) Mean (SD)	10632.4 (1731.8)	10494.5 (1569.7)
$AUC_{(0\text{-inf})}$ (ng*hr/mL) Mean (SD)	10866.9 (1762.5)	10736 (1709.3)

SD=standard deviation, hr=hour

Table 13-Statistical analysis for a single 200 mg dose of emtricitabine administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual emtricitabine capsules (reference arm)

Emtricitabine (FTC) PK parameter	Emtricitabine geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination tablet) N=15	RPV+FTC+TDF (Individual reference formulations) N=15		
C_{max} (ng/mL)	2127	2249.2	94.6	85.4%- 104.7%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	10337.7	10494.1	98.5	95.2%- 102%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	10574.1	10728.2	98.6	95.4%- 101.8%

(Analysis excludes data from subject 7)

The FDA statistical analyses evaluated emtricitabine administered as 200 mg single doses of emtricitabine under fasted conditions with fixed dose combination tablets compared to individual emtricitabine capsules. The results of the analyses were similar to the results reported by the applicant. For the fixed dose combination tablets, the 90% confidence interval for emtricitabine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%.

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Tenofovir (TDF)

Table 14-Pharmacokinetic parameters for a single 300 mg dose of tenofovir administered under fasted conditions as part of a fixed dose combination tablet and as individual tenofovir tablets

Tenofovir (TDF) PK parameter	RPV+FTC+TDF (Individual reference formulations) N=15	RPV/FTC/TDF (fixed dose combination tablet) N=16
C_{max} (ng/mL) Mean (SD)	380.6 (118.9)	359.7 (99.5)
T_{max} (hr) Median	0.75	0.75
$AUC_{(0\text{-last})}$ (ng*hr/mL) Mean (SD)	2218.4 (755.6)	2356.4 (524.5)
$AUC_{(0\text{-inf})}$ (ng*hr/mL) Mean (SD)	2426.6 (739.3)	2552.6 (522.3)

Table 15-Statistical analysis for a single 300 mg dose of tenofovir administered under fasted conditions as part of a fixed dose combination tablet (test arm) compared to individual tenofovir tablets (reference arm)

Tenofovir (TDF) PK parameter	Tenofovir geometric least square mean		Ratio (%)	90% confidence intervals
	RPV/FTC/TDF (fixed dose combination tablet) N=15	RPV+FTC+TDF (Individual reference formulations) N=15		
C_{max} (ng/mL)	335.6	360.6	93.1	79.1%-109.6%
$AUC_{(0\text{-last})}$ (ng*hr/mL)	2249.6	2060.7	109.2	91.4%-130.4%
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	2452.6	2293.4	106.9	92.5%-123.7%

(Analysis excludes data from subject 7)

The FDA statistical analyses evaluated tenofovir administered as 300 mg single doses of tenofovir under fasted conditions with fixed dose combination tablets compared to individual tenofovir tablets. The results of the analyses were similar to the results reported by the applicant except for $AUC_{(0\text{-inf})}$. The 90% confidence interval for tenofovir C_{max} and $AUC_{(0\text{-last})}$ were not within 80%-125% but the 90% confidence interval for tenofovir $AUC_{(0\text{-inf})}$ was within 80%-125%. In contrast, the applicant reported that the 90% confidence interval for tenofovir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were not within 80%-125%. However, the difference in the upper limit of the 90% confidence interval for $AUC_{(0\text{-inf})}$ when comparing the results reported by the applicant and the FDA analysis

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results is minor. The conclusions for the trial regarding tenofovir exposure for the fixed dose combination tablet when compared to the individual tenofovir tablets are unchanged because in both the FDA analysis and the applicant's analysis, the 90% confidence interval was not within 80%-125% for all three tenofovir parameters [C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$].

10.4 Safety Issues

No deaths or other serious adverse events were reported for the trial. No adverse event was reported in more than one subject.

Table 16-Summary of treatment emergent adverse events

Adverse Event Category, n (%)	FTC+RPV+TDF Reference (N=15)	FTC/RPV/TDF Test (N=16)
Any treatment-emergent AE	0	2 (12.5%)
Study drug-related treatment-emergent AE	0	2 (12.5%)
Grade 3 or 4 treatment-emergent AE	0	0
Treatment-emergent AE leading to discontinuation of study drug	0	1 (6.3%)
Any treatment-emergent SAE	0	0
Death	0	0

FTC+RPV+TDF reference = a single dose of FTC 200-mg capsule, RPV 25-mg tablet, and TDF 300-mg tablet
FTC/RPV/TDF FDC test = a single dose of FDC tablet (FTC 200 mg/RPV 25 mg/TDF 300 mg)

11. Discussion and Conclusions

Based on the results from the GS-US-264-108 trial, the following conclusions can be made based on the applicant's analysis:

- Under fasted conditions, bioequivalence was not achieved for rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ when comparing the fixed dose combination tablets to individual rilpivirine tablets. The 90% confidence interval for rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were not within 80%-125%. When rilpivirine was administered as 25 mg single doses of rilpivirine with fixed dose combination tablets under fasted conditions compared to individual rilpivirine tablets, the rilpivirine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were increased by 25%, 29%, and 25%, respectively.
- Under fasted conditions, bioequivalence was achieved for emtricitabine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ when comparing the fixed dose combination tablets to individual emtricitabine capsules. The 90% confidence interval for emtricitabine C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were within 80%-125%. When emtricitabine was administered as 200 mg single doses of emtricitabine under fasted conditions with fixed dose combination tablets compared to individual emtricitabine capsules, the

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emtricitabine C_{max} was decreased by 5%, and the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ were decreased by 2% or less.

- Under fasted conditions, bioequivalence was not achieved for tenofovir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ when comparing the fixed dose combination tablets to individual tenofovir tablets. The 90% confidence interval for tenofovir C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were not within 80%-125%. When tenofovir was administered as 300 mg single doses of tenofovir under fasted conditions with fixed dose combination tablets compared to individual tenofovir tablets, the tenofovir C_{max} was decreased by 7%, and the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ were increased by 9% and 8%, respectively.

An independent analysis by the clinical pharmacology reviewer confirmed the applicant's results and conclusions with the exception of a minor difference in the upper limit of the 90% confidence interval for tenofovir $AUC_{(0\text{-inf})}$. The difference is analysis results do not alter the trial's conclusions regarding tenofovir exposure for the fixed dose combination tablet when compared to the individual tenofovir tablets. Both the applicant's analysis and the FDA analysis support the conclusion that under fasted conditions only the emtricitabine component of the fixed dose combination tablet achieved bioequivalence for C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ when comparing the fixed dose combination tablet to the individual reference formulations.

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/s/

STANLEY AU
07/15/2011

SARAH M ROBERTSON
07/15/2011

BIOPHARMACEUTICS FILLING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-123	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	February 10, 2011		
Division:	Division of Anti-Infective & Ophthalmology Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Gilead	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	To be determined	**Date Assigned:**	February 10, 2011
Generic Name:	Emtricitabine/ Rilpivirine HCl/ Tenofovir Disoproxil Fumarate	**Date of Review:**	March 14, 2011
Indication:	For use as a complete regimen for the treatment of HIV-1 infection in adults.	**Type of Submission:** Resubmission of New Drug Application after Refuse to File of Original Application.	
Formulation/ strengths	Fixed-Dose Combination (FDC) Tablet/ 200 mg/25 mg/300 mg		
Route of Administration	Oral		

SUBMISSION:

This rolling 505(b)(1) New Drug Application is for an immediate release fixed-dose combination tablet of emtricitabine/ rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF) for the treatment of HIV-1 infection in adults. Emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) are antiretroviral agents of the nucleoside reverse transcriptase inhibitor (N(t)RTI) class developed by Gilead that have been approved for the treatment of HIV-1 infection as stand-alone agents or in fixed-dose combination products with the following trade names: Emtriva®(emtricitabine), Viread®(tenofovir DF), Truvada®(emtricitabine/tenofovir DF) and Atripla® (efavirenz/ emtricitabine/tenofovir DF). Rilpivirine is an investigational agent of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class for which NDA 202-022 has been filed on 23 July 2010 by Gilead's corporate partner Tibotec Inc.

Four drug product formulations were investigated during the drug product development. All 4 formulations were tested for bioequivalence to the reference drugs under fed conditions. Only formulation 3 [redacted] (b) (4) showed bioequivalence to the reference drug products for all 3 components. Formulation 3 is the proposed commercial formulation.

BIOPHARMACEUTICS:

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criteria for emtricitabine, rilpivirine HCl, and tenofovir disoproxil fumarate. This submission includes a dissolution method development report and proposed dissolution specifications for all 3 active ingredients as follows:

Proposed dissolution method: This method is for the dissolution testing of emtricitabine/ rilpivirine/ tenofovir DF (FTC/RPV/TDF) tablets using a USP Type 2 apparatus operated at 75 rpm and 0.5% polysorbate 20 in 0.01 N HCl as dissolution medium. [redacted] (b) (4) [redacted] (b) (4). The amount of FTC, RPV, and TDF dissolved are determined by HPLC or UPLC using external standard analysis.

Proposed dissolution acceptance criteria: The amount of emtricitabine and tenofovir DF dissolved is not less than [redacted] (b) (4) (Q) at 30 minutes and the amount of rilpivirine dissolved is not less than [redacted] (b) (4) (Q) at 60 minutes.

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed NDA 202-123 for filing purposes. We found this NDA filable from a biopharmaceutics perspective. The sponsor has submitted a reviewable submission. There are no comments to be conveyed to the sponsor at this time.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc. P. Marroum

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/s/

ELSBETH G CHIKHALE
03/14/2011

ANGELICA DORANTES
03/14/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202-123**	**Brand Name**	**Complera**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**Emtricitabine/rilpivirine/ tenofovir disoproxil**
Medical Division	**DAVP**	**Drug Class**	**NNRTI/NRTI**
OCP Reviewer	**Stanley Au**	**Indication(s)**	**Treatment of HIV-1 infection**
OCP Team Leader	**Sarah Robertson**	**Dosage Form**	**Oral tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**200 mg/25 mg/300 mg once daily**
Date of Submission	**February 10, 2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**July 10, 2011**	**Sponsor**	**Gilead**
Medical Division Due Date	**July 24, 2011**	**Priority Classification**	**Priority**
PDUFA Due Date	**August 10, 2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Critical Comments If any
STUDY TYPE			
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**		
Tabular Listing of All Human Studies			
HPK Summary			
Labeling	**X**		
Reference Bioanalytical and Analytical Methods	**X**	**1) Validation reports: 4** **2) Bioanalytical reports: 6**	
I. Clinical Pharmacology			
Mass balance:			
Isozyme characterization:			
Blood/plasma ratio:			
Plasma protein binding:			
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:			
multiple dose:			
Patients-			
single dose:			
multiple dose:			
Dose proportionality -			
fasting / non-fasting single dose:			
fasting / non-fasting multiple dose:			
Drug-drug interaction studies -			
In-vivo effects on primary drug:			
In-vivo effects of primary drug:			

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In-vitro:			
Subpopulation studies -			
ethnicity:			
gender:			
pediatrics:			
geriatrics:			
renal impairment:			
hepatic impairment:			
PD -			
Phase 2:			
Phase 3:			
PK/PD -			
Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:			
Population Analyses -			
Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:			
Bioequivalence studies -			
traditional design; single / multi dose:	**X**	**3**	
replicate design; single / multi dose:			
Food-drug interaction studies			
Bio-waiver request based on BCS			
BCS class			
Dissolution study to evaluate alcohol induced dose-dumping			
III. Other CPB Studies			
Genotype/phenotype studies			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		**3**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			The to be marketed emtricitabine/rilpivirine/ tenofovir disoproxil fixed dose combination tablet was compared to the individual commercial formulations for tenofovir and emtricitabine and the rilpivirine formulation used in the Phase 3 trials.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

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4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate			X	

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	effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___YES_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Reference ID: 2908639

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/s/

STANLEY AU
02/22/2011

SARAH M ROBERTSON
02/22/2011