CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-752

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21500	Submission Date(s): 31March2004
Brand Name	TRUVADA®
Generic Name	Tenofovir disoproxil fumarate/Emtricitabine
Reviewer	Jennifer L. DiGiacinto, Pharm.D.
Team Leader	Kellie Reynolds, Pharm.D.
OCPB Division	DPE III
OND Division	DAVDP
Applicant	Gilead
Relevant IND(s)	IND 21-752
Submission Type; Code	Priority (1P)
Formulation; Strength(s)	Tenofovir disoproxil fumarate 300-mg/Emtricitabine 200-mg Combination Tablet
Indication	Treatment of HIV infection in combination with other antiretroviral drugs

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1. EXECUTIVE SUMMARY

Tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are nucleoside reverse transcriptase inhibitors (NRTI), which are currently approved as separate formulations for the treatment of HIV infection in adults at least 18 years of age. The applicant has developed a new combination tablet (CT) combining both compounds into one tablet (TDF 300-mg/FTC 200-mg). In support of this NDA, the Applicant adequately addressed the following issues:

- The CT is BE to the currently marketed TDF 300-mg tablet and the currently marketed FTC 200-mg capsule
- No clinically significant food effect is observed with the CT regardless of the content of the meal (high-fat or light meal) (GS-US-104-172).
- Absence of a drug-drug interaction between TDF and FTC (FTC-114).

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to this submission.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

TDF and FTC are co-formulated as a TDF/FTC CT containing 300-mg of TDF and 200-mg of FTC, which will be administered once daily as part of an antiretroviral regimen. This NDA contains a pivotal BE study (GS-US-104-172), a previously submitted and reviewed TDF + FTC drug-drug interaction study (FTC-114), and dissolution data for the new CT formulation.

GS-US-104-172 is the pivotal bioequivalence (BE) study that compares the new CT of TDF/FTC to TDF and FTC administered concurrently as a separate tablet and capsule. In addition, this study also investigates the food effect for the CT with a high fat meal and a light meal. This was an open-label, randomized, four-way crossover, pharmacokinetic (PK) study in 44 healthy volunteers. The results of this pivotal BE study demonstrated that the administration of TDF/FTC CT resulted in plasma-concentration-time profiles of TDF and FTC similar to those after the concurrent administration of the two separate formulations. In accordance with the FDA Bioavailability (BA) and BE Studies for Orally Administered Drug Products Guidance, BE with respect to formulation is concluded if the 90% CI for the ratio (test to reference) falls within 80% to 125% for C_{max} and AUC_{0-t} and AUC_{0-inf}. TDF/FTC CT (test product) met the BE definition when compared to the separate formulations of TDF and FTC (reference products). See table below.

Geometric Least Square Mean Ratios and 90% Confidence Interval (CI) for TDF and FTC Administered as the Combination Tablet and Marketed Formulations Concurrently (GS-US-104-172)

TDF	**Geometric Least Square Mean Ratio (90%)**		
TDF/FTC CT / TDF + FTC	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
	94.0 (85.8-103.0)	100.0 (94.0-106.5)	100.3 (94.6-106.3)
FTC	**Geometric Least Square Mean Ratio (90%)**		
TDF/FTC CT / TDF + FTC	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
	96.5 (89.5-104.0)	100.1 (95.9-104.5)	100.2 (96.2-104.4)

Data Source: Table from Module 2, Volume 2, Table 3 in the NDA submission.

The food effect assessment of GS-US-104-172 investigated the effect of a high-fat meal or a light meal on the PK parameters (C_{max} and AUC) of TDF and FTC administered as the CT. The study results show the administration of the CT after either a high-fat meal or a light meal delays the time to TDF maximum concentration (T_{max}) by approximately 0.75 hours. The light meal and the high-fat meal caused similar increases in TDF AUC and C_{max}. The C_{max} of TDF increases by approximately 15%, relative to the fasted state, and TDF AUC_{0-inf} increases by approximately 35%. FTC concentrations were unaffected by either meal type.

When the food effect results of GS-US-104-172 are compared to previous food effect study data for TDF, the high-fat meal results are similar (GS-00-914). The increases in TDF exposures after a light meal differ from previous results reported with VIREAD after a light meal. In this study after a light meal, TDF AUC and C_{max} increases of approximately 34% and 13.5% were seen in comparison to no significant increases seen with TDF administered as VIREAD. The reason for these differences could be attributed to VIREAD light meal data were cross study comparisons and the TRUVADA light meal data were not. The increases in TDF concentrations are not clinically relevant because previous VIREAD safety and efficacy studies were conducted under fed conditions. Therefore, the TDF/FTC CT can be taken without regard to food.

Since the approval of NDA 21-752 was based on a pivotal BE study, an inspection of the clinical trial site and the analytical laboratory site was conducted by the Division of Scientific Investigations (DSI). The pivotal BE study (GS-US-104-172) also contained the food effect analysis. Following the inspection at the clinical trial site, a Form 483 was issued for the food effect portion of GS-US-104-172. After further internal discussions, a decision was made to accept the food effect data. The rationale behind this decision can be found in the GS-US-104-172 Study Review located in the Appendix section of this report.

FTC-114 is an open-label, randomized, three-way crossover study that evaluates the steady-state PK of FTC and TDF when administered alone and in combination in healthy volunteers. This study was originally submitted and reviewed with the EMTRIVA NDA (21-500). These data indicate TDF has no clinically significant effect on the PK of FTC when the two drugs are administered together for 7 days and FTC has no effect on the PK of TDF when the two drugs are administered together for 7 days.

The dissolution of TDF/FTC CT is assessed using USP II Apparatus with operated at . The dissolution medium is 900 mL of 0.01 N HCl maintained at 37° C. The amounts of TDF and FTC dissolved are determined by The single time-point specification of dissolved at 30 minutes is proposed for TDF/FTC tablets (Q= dissolved in 30 minutes).

This dissolution method and proposed specification takes into consideration the following:

- TDF is a BCS Class 3 drug having a high solubility and low permeability and FTC is a BCS Class 1 drug having a high solubility and high permeability.
- The dissolution method selection provides discriminatory power to detect manufacturing process variations.
- The dissolution data obtained to date for TDF/FTC tablets.

- The applicant proposed a specification of — dissolved at 30-minutes. The proposed dissolution method and specification for TRUVADA are acceptable.

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

2.1 General Attributes of the Drug
Not applicable.

2.2 General Clinical Pharmacology
Not applicable.

2.3 Intrinsic Factors
Not applicable.

2.4 Extrinsic Factors
Not applicable.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

TDF is a BCS class 3 compound with high solubility and a low permeability. A drug substance is classified as highly soluble when the highest dose strength is soluble in ≤ 250 mL of aqueous media over the pH range of 1.0 -8.0. TDF has an intrinsic solubility of 8.5 mg/mL. Therefore, the solubility volume of TDF 300-mg tablets is —. The permeability class of TDF was determined using an *in vitro* epithelial cell culture method with TC-7 cell monolayers (TC-7 cell is a subclone of the Caco-2 cell line). The permeation coefficient of TDF was 6.7×10^{-7} cm/sec under standard conditions. In comparison, a drug classified as having a high permeability, — had a permeation coefficient of 2.5×10^{-5} cm/sec. This value compared well with the literature value for — of 3.5×10^{-5} cm/sec. Based on this comparison, TDF is a low permeability drug. A BCS Class 3 drug is not expected to have a correlation between *in vitro* dissolution and *in vivo* absorption.

FTC is a BCS class 1 compound with a high solubility and a high permeability. FTC has an intrinsic solubility of 119 mg/mL and the solubility volume for a 200-mg dose of FTC is less than 2 mL. Although the permeability of FTC has never been measured, it is nearly completely absorbed with an oral bioavailability (BA) of 93% in human subjects. Based on this observation, FTC is a high permeability drug. Because FTC is a BCS Class 1 drug, a correlation between *in vitro* dissolution and *in vivo* absorption is also not expected.

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

The clinical (TDF/FTC tablets used in the pivotal bioequivalence (BE) study GS-US-104-0172) and the proposed commercial formulation of TDF/FTC tablets are identical. GS-US-104-172 compares the new CT of TDF/FTC to TDF and FTC administered concurrently. In addition, this study also investigates the food effect for the CT with a high fat meal and a light meal.

The summary statistics for TDF PK parameters are listed below.

Summary of TDF PK Parameters

TDF PK Parameter	Treatment A[a] (N=39) Arithmetic Mean (%CV)	Treatment B[b] (N=39) Arithmetic Mean (%CV)
C_{max} (ng/mL)	267.59 (30.1)	253.63 (32.9)
T_{max} (h)[c]	0.75 (0.50, 2.50)	0.75 (0.50, 2.50)
T½ (h)	17.51 (24.0)	16.48 (25.0)
AUC_{0-t} (ng·h/mL)	1593.06 (29.2)	1605.84 (33.3)
AUC_{0-inf} (ng·h/mL)	1944.98 (26.2)	1961.07 (30.3)

[a] Treatment A = coadministration of TDF and FTC to fasted subjects
[b] Treatment B = TDF/FTC CT administered to fasted subjects
[c] Median (min, max)
Data Source: Section 15, Tables 11 and 12

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

90% Confidence Interval for Geometric Mean Ratios of TDF PK Parameters for Treatment B versus Treatment A

TDF PK Parameter	Geometric Least Square Means		Geometric Mean Ratio (%)	90% Confidence Interval
	TX B[a] (N=39)	TX A[b] (N=39)		
C_{max}	240.90	256.20	94.0	85.8-103.0
AUC_{0-t}	1505.30	1505.00	100.0	94.0-106.5
AUC_{0-inf}	1854.08	1848.43	100.3	94.6-106.3

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment A = Coadministration of TDF and FTC to fasted subjects
Data Source: Section 15, Table 19

The summary statistics of FTC PK parameters are listed below.

Summary of FTC PK Parameters

FTC PK Parameter	Treatment A[a] (N=38) Mean (%CV)	Treatment B[b] (N=39) Mean (%CV)
C_{max} (µg/mL)	2.21 (26.7)	2.31 (26.0)
T_{max} (h)[c]	1.25 (0.75, 3.00)	1.50 (0.75, 3.00)
T½ (h)	15.31 (25.0)	15.64 (23.3)
AUC_{0-t} (µg·h/mL)	10.39 (20.1)	10.32 (20.6)
AUC_{0-inf} (µg·h/mL)	10.70 (20.0)	10.62 (20.2)

[a] Treatment A = coadministration of TDF and FTC to fasted subjects
[b] Treatment B = TDF/FTC CT administered to fasted subjects
[c] Median (min, max)
Data Source: Section 15, Tables 15 and 16

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

90% Confidence Interval for Geometric Mean Ratios of FTC PK Parameters for Treatment B versus Treatment A

FTC PK Parameter	Geometric Least Square Means		Geometric Mean Ratio (%)	90% Confidence Interval
	TX B[a] (N=39)	TX A[b] (N=39)		
C_{max}	2.03	2.11	96.5	89.5 -104.0
AUC_{0-t}	10.11	10.10	100.1	95.9 -104.5
AUC_{0-inf}	10.42	10.40	100.2	96.2 -104.4

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment A = Coadministration of TDF and FTC to fasted subjects
Data Source: Section 15, Table 22

The TDF/FTC CT (TRUVADA) is BE to the TDF single tablet (VIREAD) and the FTC single capsule (EMTRIVA).

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

The summary statistics of TDF PK parameters for the food effect assessment in study GS-US-104-172 are listed below.

Food Effect on PK of TDF Administered as the TDF/FTC CT to Fasted and Fed Subjects

TDF PK Parameter	Treatment B[a] (N=39) Mean (%CV)	Treatment C[b] (N=39) Mean (%CV)	Treatment D[c] (N=39) Mean (%CV)
C_{max} (ng/mL)	253.63 (33.0)	293.62 (29.9)	290.17 (33.2)
T_{max} (h)[d]	0.75 (0.50, 2.50)	1.50 (0.50, 4.00)	1.50 (0.50, 4.00)
AUC_{0-t} (ng·h/mL)	1605.84 (33.3)	2246.78 (26.9)	2207.18 (26.1)
AUC_{0-inf} (ng·h/mL)	1961.07 (30.3)	2581.82 (24.9)	2561.12 (24.6)

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment C = TDF/FTC combination tablet administered with a high-fat meal
[c] Treatment D = TDF/FTC combination tablet administered with a light meal
[d] Median (min, max)
Data Source: Section 15, Tables 12, 13, and 14

The food effect GLS and 90% CI values for TDF are listed below.

Food Effect on PK of TDF Administered as the TDF/FTC CT

TDF PK Parameters	Geometric Least Square Means			TX C : TX B		TX D : TX B	
	TX B[a] (N=39)	TX C[b] (N=39)	TX D[c] (N=39)	GMR[d] (%)	90% CI	GMR[d] (%)	90% CI
C_{max}	240.90	279.52	273.36	116.0	105.9-127.1	113.5	103.6-124.3
AUC_{0-t}	1505.30	2162.02	2115.57	143.6	134.9-152.9	140.5	132.0-149.6
AUC_{0-inf}	1854.08	2499.27	2481.29	134.8	127.2-142.9	133.8	126.2-141.9

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment C = TDF/FTC combination tablet administered with a high-fat meal
[c] Treatment D = TDF/FTC combination tablet administered with a light meal
[d] GMR= Geometric Mean Ratio
Data Source: Section 15, Tables 20 and 21

Regardless of the meal content (high-fat or light meal), a food effect does occur with TDF portion of the CT. TDF $AUC_{0\text{-}inf}$ and C_{max} increase approximately 35% and 15%, respectively, in a fed state (either meal) as compared to TDF in a fasted state. These increases seen in AUC and C_{max} after a high-fat meal are similar to what has been reported with VIREAD (TDF single tablet). The increases in TDF exposures after a light meal differ with previous results reported with VIREAD after a light meal. The reason for these differences could be attributed to VIREAD light meal data were cross study comparisons and the TRUVADA light meal data were not. The increases in TDF concentrations are not clinically relevant because previous VIREAD safety and efficacy studies were conducted under fed conditions.

No food effect exists for FTC in the TDF/FTC CT regardless of the meal contents. These results are similar to results seen with EMTRIVA.

The TDF/FTC CT can be taken without regard to food.

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

Proposed Dissolution Method and Specification
The proposed dissolution method for Truvada® (TDF 300-mg/FTC 200-mg tablet) is as follows:

Apparatus	USP 2
Rotation Speed	
Temperature:	37.5° C ± 0.5° C
Medium:	900 mL of 0.01 N HCl
Sampling Time:	30 minutes
Sample Amount:	One tablet per vessel
Filter:	filter
Sample Volume:	10 mL
Analytical Method:	

The proposed dissolution specification for Truvada® TDF 300-mg/FTC 200-mg tablet is Q = dissolved in 30 minutes.

The proposed dissolution method and specification are acceptable.

2.6 Analytical Section
Not applicable.

3. LABELING RECOMMENDATIONS

CLINICAL PHARMACOLOGY

The applicant has combined labeling information from VIREAD and EMTRIVA labels to create the TRUVADA label. The identical drug-drug interaction tables from the VIREAD and EMTRIVA labels will be included into the TRUVADA label in this section of the label.

WARNINGS
Renal Impairment

Tenofovir and emtricitabine are principally eliminated by the kidney. Dosing interval adjustment of TRUVADA is recommended in all patients with creatinine clearance 30-49 mL/min, (see DOSAGE AND ADMINISTRATION). TRUVADA should not be administered to patients with creatinine clearance <30 mL/min or patients requiring hemodialysis.

PRECAUTIONS

Drug Interactions

All drug interaction information that is in the most recent Viread and Emtriva labels will be included in this section.

DOSAGE AND ADMINISTRATION

The dose of TRUVADA is one tablet (containing 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine) once daily taken orally with or without food.

Dose Adjustment for Renal Impairment:

Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥50	30–49	<30 (Including Patients Requiring Hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

[a] Calculated using ideal (lean) body weight.

HOW SUPPLIED

TRUVADA is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil) and 200 mg of emtricitabine. The tablets are blue, capsule-shaped, film-coated, debossed with "GILEAD" on one side and with "701" on the other side. Each bottle contains 30 tablets (NDC 61958-0701-1) and a desiccant (silica gel canister or sachet) and is closed with a child-resistant closure.

Store below 86 F (30 °C).

- Keep container tightly closed.

- Dispense only in original container.

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cc: HFD-530 /NDA 21-752
/MO/Fleischer
PM/O'Neill
HFD-880 /JDiGiacinto
HFD-880 /TL/KReynolds

4. Appendices

4.1 Individual Study Reviews

4.1.1 Dissolution Study

Proposed Dissolution Method and Specification
The proposed dissolution method for Truvada® (TDF 300-mg/FTC 200-mg tablet) is as follows:

Apparatus	USP 2
Rotation Speed	
Temperature:	37.5° C ± 0.5° C
Medium:	900 mL of 0.01 N HCl
Sampling Time:	30 minutes
Sample Amount:	One tablet per vessel
Filter:	
Sample Volume:	10 mL
Analytical Method:	

The proposed dissolution specification for Truvada® TDF 300-mg/FTC 200-mg tablet is Q = dissolved in 30 minutes.

Background
Solubility/Dissociation Constant
Tenofovir disoproxil free base (TDF) has a pKa of 3.75 with an intrinsic aqueous solubility of 8.5 mg/mL at room temperature. Emtricitabine (FTC) has a pKa of 2.65 with an intrinsic aqueous solubility of 119 mg/mL at room temperature.

Biopharmaceutics Classification System (BCS)
TDF is a BCS class 3 compound with high solubility and a low permeability. A drug substance is classified as highly soluble when the highest dose strength is soluble in ≤ 250 mL of aqueous media over the pH range of 1.0 -8.0. TDF has an intrinsic solubility Therefore, the solubility volume of TDF 300-mg tablets is The permeability class of TDF was determined using an *in vitro* epithelial cell culture method with TC-7 cell monolayers (TC-7 cell is a subclone of the Caco-2 cell line). The permeation coefficient of TDF was 6.7×10^{-7} cm/sec under standard conditions. In comparison, a drug classified as having a high permeability, had a permeation coefficient of 2.5×10^{-5} cm/sec. This value compared well with the literature value for of 3.5×10^{-5} cm/sec. Based on this comparison, TDF is a low permeability drug. A BCS Class 3 drug is not expected to have a correlation between *in vitro* dissolution and *in vivo* absorption.

FTC is a BCS class 1 compound with a high solubility and a high permeability. FTC has an intrinsic solubility of 119 mg/mL and the solubility volume for a 200-mg dose of FTC is less than 2 mL. Although the permeability of FTC has never been measured, it is nearly completely absorbed with an oral bioavailability (BA) of 93% in human subjects. Based on this observation, FTC is a high permeability drug. Because FTC is a BCS Class 1 drug, a correlation between *in vitro* dissolution and *in vivo* absorption is also not expected.

Dissolution Test Method Justification

Study Design

Experimental batches of TDF/FTC tablets were produced to evaluate the effect of the tablet hardness and percent coating on tablet dissolution. The tablet hardness ranged from [redacted] The tablets were film-coated to a weight gain ranging from [redacted]. The values for tablet hardness and percent coating reflect the in-process acceptance criteria for commercial manufacturing. The targets for tablet hardness and percent weight gain are [redacted] and [redacted], respectively.

Dissolution studies were performed at pH 1.2 [redacted], pH 2.0 (0.01 N HCl), pH 4.5 [redacted] acetate buffer), and pH 6.8 ([redacted] phosphate buffer). Since the dose solubility volume for TDF and FTC [redacted] pH range studied. The percent of TDF and FTC dissolved were determined at 10, 20, 30, and 45 minutes to establish a dissolution profile.

Experimental Batches

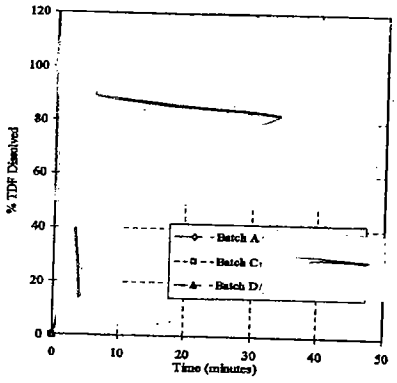
Experimental Batches of TDF/FTC Tablets Used to Assess Tablet Dissolution

Lot Number	Referenced As	Hardness (Kp)	Tablet Coating (% wt. Gain)
F1344-004	Batch A		
F1344-004	Batch B		
F1344-005	Batch C		
F1344-006	Batch D		
F1344-006	Batch E		

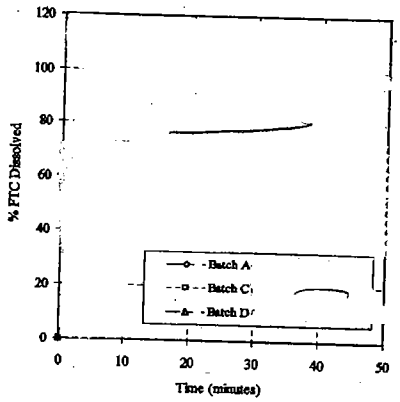
Effect of Tablet Hardness on Dissolution

The effect of tablet hardness on the dissolution of TDF/FTC tablets was evaluated by comparing the dissolution profiles of three batches compressed to three different tablet hardness. A pH of 2.0 dissolution media was used for these studies. The dissolution profiles for both compounds are shown below.

Effect of Hardness on Dissolution of TDF in TDF/FTC Tablets at pH 2.0



Effect of Hardness on Dissolution of FTC in TDF/FTC Tablets at pH 2.0

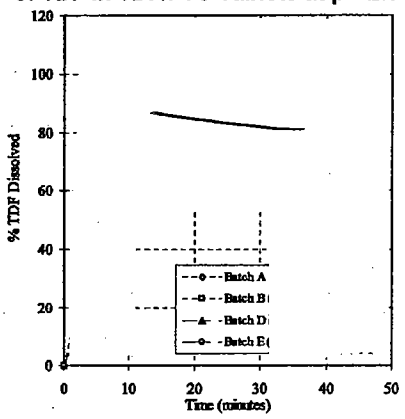


The dissolution profiles for both TDF and FTC show a decrease in mean percent dissolved at 10 minutes as tablet hardenss increases. Complete dissolution is achieved at the subsequent 30 and 45 minute time points regardless of tablet hardness.

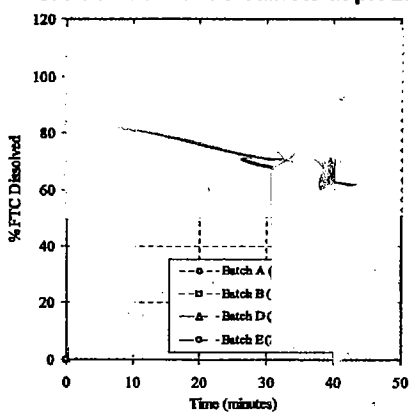
Effect of Percent Coating Weight on Dissolution

The effect of weight percent of coating on tablet dissolution was evaluated Tablets compressed to a hardness of ——— were each film-coated to ——— by weight. Dissolution profiles were obtained using pH 2.0 dissolution medium. The dissolution profiles for both compounds are shown below.

Effect of Tablet Coating on Dissolution of TDF in TDF/FTC Tablets at pH 2.0



Effect of Tablet Coating on Dissolution of FTC in TDF/FTC Tablets at pH 2.0

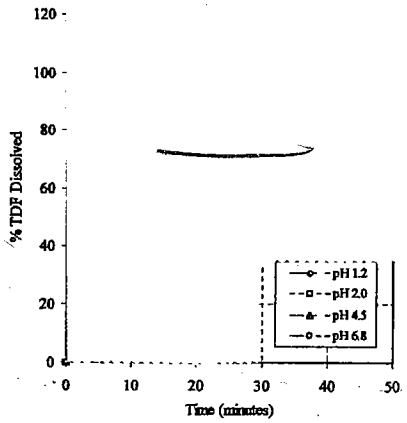


The data show that weight percent coating does not affect the dissolution profiles of TDF/FTC tablets compressed to the low and high limits of the target hardness range.

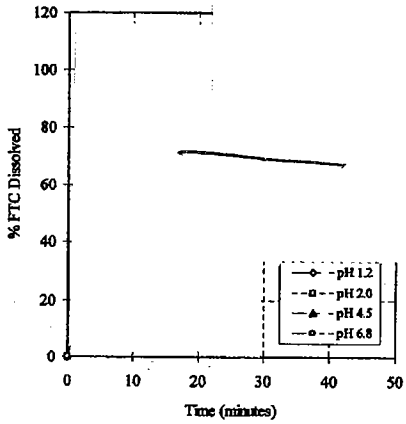
Effect of Dissolution Media pH on Dissolution

Dissolution profiles for two batches of tablets compressed to —) (Batch A) and ——— (Batch E) were obtained using dissolution media pH 1.2, 2.0, 4.5, and 6.8. The dissolution profiles for both compounds from both batches are shown below.

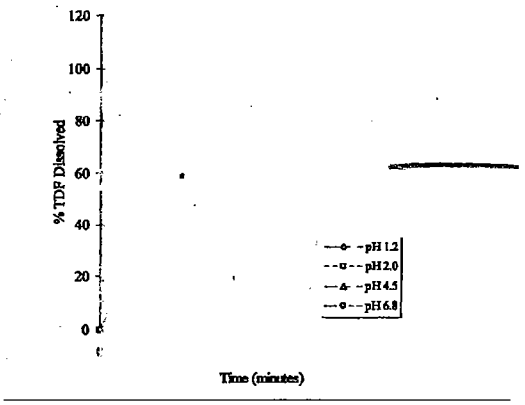
Effect of Dissolution Media pH on Dissolution on TDF in TDF/FTC Tablets, Batch A, ———



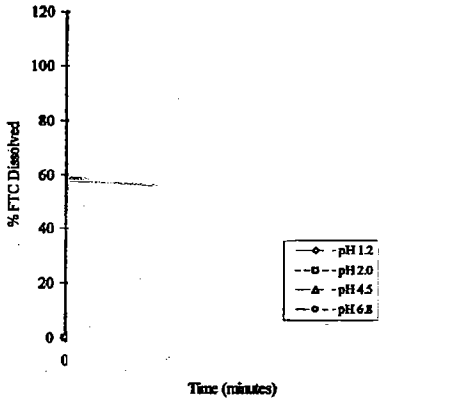
Effect of Dissolution Media pH on Dissolution on FTC in TDF/FTC Tablets, Batch A, ———



Effect of Dissolution Media pH on Dissolution of TDF in TDF/FTC Tablets, Batch E,



Effect of Dissolution Media pH on Dissolution of FTC in TDF/FTC Tablets, Batch E,



No measurable difference in dissolution profile was observed as a function of the dissolution media pH regardless of tablet hardness. As the tablet dissolution was unaffected over the pH range studied, the primary consideration for selecting the pH of the dissolution media was the stability of TDF and FTC in solution. TDF is the least stable of the two drug substances in solution andTDF is most stable in the pH range of 2 to 3. Therefore; a pH of 2.0 for the dissolution media was selected for the dissolution test of TDF/FTC tablets.

Reviewer Comment: The Sponsor's selection of 0.01 N HCl (pH 2.0) as the dissolution medium for the TDF/FTC tablet is acceptable.

In Vitro Dissolution of Clinical Formulations

The clinical (TDF/FTC tablets used in the pivotal bioequivalence (BE) study GS-US-104-0172) and the proposed commercial formulation of TDF/FTC tablets are identical. Provided in the tables below are the mean and individual tablet dissolution data of 12 tablets each from four primary stability batches (Lots V301B, V302B, V303B, and V304B) of TDF/FTC tablets. Lot V301B was used in the BE study GS-US-104-0172. The data indicate that the dissolution of TDF and FTC are nearly complete at the 30 minute time point for all of the lots examined.

Dissolution Profiles of the Primary Stability Lots of TDF/FTC Tablets

Lot V301B	Percent Tenofovir DF Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	69	92	95	95
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	10.5	4.1	2.9	2.9

Lot V301B	Percent Emtricitabine Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	65	90	95	97
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	13.0	7.2	4.2	3.4

Lot V302B	Percent Tenofovir DF Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	58	87	93	93
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	10.5	4.6	3.2	2.9

Lot V302B	Percent Emtricitabine Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	56	86	93	95
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	11.8	7.7	4.7	3.6

Dissolution Profiles of the Primary Stability Lots of TDF/FTC Tablets, Continue

Lot V303B	Percent Tenofovir DF Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	70	92	95	96
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	10.6	4.1	2.2	1.9

Lot V303B	Percent Emtricitabine Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	66	89	94	96
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	12.3	6.8	3.5	2.8

Lot V304B	Percent Tenofovir DF Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	54	86	94	95
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	6.9	6.0	2.0	2.1

Lot V304B	Percent Emtricitabine Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
Mean	52	83	94	96
Tablet 1				
Tablet 2				
Tablet 3				
Tablet 4				
Tablet 5				
Tablet 6				
Tablet 7				
Tablet 8				
Tablet 9				
Tablet 10				
Tablet 11				
Tablet 12				
Std. Dev.	8.2	8.1	3.4	2.6

Batch Analyses
An overview of batch manufacturing information and the usage of each TDF/FTC tablet batch released to date is presented in the table below.

Lot Number	Batch Size (kg)	Date of Manufact.	Manufact. & Packaging Site	Use
V301B		04/03		Clinical & Primary Stability
V302B		06/03		Clinical & Primary Stability
V303B		07/03		Clinical & Primary Stability
V304B		09/03		Clinical & Primary Stability
V305B		10/03		Clinical & Scale-Up
V306B		11/03		Clinical, Scale-Up & Primary Stability
V308B		11/03		Clinical, Scale-Up & Primary Stability

Assessment/Conclusion
The dissolution of TDF/FTC tablets is assessed using USP II Apparatus with ——— operated at ——— . The dissolution medium is 900 mL of 0.01 N HCl maintained at 37° C. The amounts of TDF and FTC dissolved are determined by ——————— HPLC. The single time-point specification of —— dissolved at 30 minutes is proposed for TDF/FTC tablets (Q= —— dissolved in 30 minutes).

This dissolution method and proposed specification takes into consideration the following:

- TDF is a BCS Class 3 drug having a high solubility and low permeability and FTC is a BCS Class 1 drug having a high solubility and high permeability.
- The dissolution method selection provides discriminatory power to detect manufacturing process variations.
- The dissolution data obtained to date for TDF/FTC tablets.

The FDA guidance document "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" states that for Class 1 and 3 drugs, dissolution is not the rate-controlling step for BA. Therefore, the dissolution test method and specification are used primarily to monitor drug product batch-to -batch variability.

Taking in consideration the guidance, the discrimination power of the assay, and the data available, an acceptance of —— dissolved at 30-minutes has been established.

Reviewer Comment: The dissolution specification for TRUVADA® (TDF 300-mg/FTC 200-mg tablets) of Q = —— dissolved in 30 minutes is acceptable.

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4.1.2 Bioavailability & Bioequivalence Studies

Pivotal BE Study (GS-US-104-172)

The FDA approved tenofovir disoproxil fumarate (TDF) for the treatment of HIV-1 infection on October 26th, 2001. Emtricitabine (FTC) received its approval for treatment of HIV-1 infection on July 2, 2003. They are both nucleoside reverse transcriptase inhibitors (NRTIs) that are administered once daily (TDF 300-mg QD and FTC 200-mg QD).

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

GS-US-104-172 is the pivotal bioequivalence (BE) study that compares the new CT of TDF/FTC to TDF and FTC administered concurrently. In addition, this study also investigates the food effect for the CT with a high fat meal and a light meal.

Study Design
This was an open-label, randomized, four-way crossover, pharmacokinetic (PK) study in healthy volunteers that evaluated the BE of TDF/FTC CT compared to TDF and FTC administered concurrently and the effect of food on the absorption of the TDF/FTC CT. Forty-four healthy male and female subjects were initially enrolled into the study and 39 subjects completed the study. A seven-day washout period separated each treatment period.

Study Treatments
- Treatment A: TDF 300-mg (single tablet) + FTC 200-mg (single capsule) administered in a fasted state
- Treatment B: TDF 300-mg/FTC 200-mg CT, administered in a fasted state
- Treatment C: TDF 300-mg/FTC 200-mg CT, administered in a fed state (high-fat meal)
- Treatment D: TDF 300-mg/FTC 200-mg CT, administered in a fed state (light meal)

Test/Reference Products and Lot #s
- **Test Product: TRUVADA**, CT of TDF/FTC (300-mg/200-mg), Lot # V301B2
- **Reference Product: VIREAD**, single tablet of TDF (300-mg), Lot # J110B1 and **EMTRIVA**, single capsule of FTC (200-mg), Lot # W303A1

Meal Macronutrient Composition

Macronutrient	High-Fat Meal	Light-Meal
Carbohydrate	57.56 grams	61.3 grams
Protein	31.5 grams	10.6 grams
Fat	48.6 grams	8.2 grams

Total caloric intake for the high-fat meal was 784 calories and the total caloric intake for the light meal was 373 calories.

Study Demographics

Characteristic	Total (N=44) N (%)
Gender:	
M	26(59.1)
F	18(40.9)
Race:	
White	19(43.2)
Black	7(15.9)
Hispanic	18(40.9)

The mean (range) age for study subjects was 43.6 years (18.9, 60.1) and study subjects mean (range) weight and height were 168.2 pounds (125, 234) and 65.9 inches (59, 72).

PK Sampling

Serial blood samples for the determination of plasma TDF and FTC concentrations were collected at pre-dose (time 0) and then 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-dose.

PK Data Analysis

- The PK parameters for TDF and FTC were assessed using noncompartmental methods (WinNonlin Version 3.3).
- All pharmacokinetic parameters for BE and food effect treatment arms were analyzed using analysis of variance (ANOVA).
- For the assessment of formulation BE, a 90% CI was obtained for the geometric mean ratio (Treatment A as reference product and Treatment B as test product).
- BE was concluded if the 90% CI intervals were within the 80-125% range for C_{max} and AUC.
- For the assessment of food effect, a 90% CI was obtained for the geometric mean ratio (Treatment B as reference and Treatment C and Treatment D as test).
- No food effect was concluded if the 90% CI intervals were within the 80-125% range for C_{max} and AUC.

GS-US-104-172 Assay Validation

Concentrations of TDF and FTC in human plasma samples collected during GS-US-104-172 were determined using Good Laboratory Practice methods (GLP) and a validated liquid chromatography, [redacted] method. The assay is acceptable. The assay characteristics for this study are listed below.

Parameter	TDF	FTC
Linear Range	[redacted]	[redacted]
LLOQ	[redacted]	[redacted]
Stability (freeze-thaw)	Stable for 66-days when frozen at -22 C°	Stable for 522-days when frozen at -80 C°
Specificity	[redacted]	
QC sample concentrations	[redacted]	

Analyte	Intra-day Accuracy N = 4	Intra-day Precision N = 4	Inter-day Accuracy N = 4	Inter-day Precision N = 4
TDF	Bias = [redacted]	%CV = 2.24 to 8.33	Bias = [redacted]	%CV = 4.37 to 7.85
FTC	Bias = [redacted]	%CV = 2.44 to 7.44	Bias = [redacted]	%CV = 3.98 to 9.47

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

Reviewer Comment: The assay is acceptable.

GS-US-104-172 Study Results

The summary statistics of TDF PK parameters are listed below.

Summary of TDF PK Parameters

TDF PK Parameter	Treatment A[a] (N=39) Arithmetic Mean (%CV)	Treatment B[b] (N=39) Arithmetic Mean (%CV)
C_{max} (ng/mL)	267.59 (30.1)	253.63 (32.9)
T_{max} (h)[c]	0.75 (0.50, 2.50)	0.75 (0.50, 2.50)
T½ (h)	17.51 (24.0)	16.48 (25.0)
AUC_{0-t} (ng·h/mL)	1593.06 (29.2)	1605.84 (33.3)
AUC_{0-inf} (ng·h/mL)	1944.98 (26.2)	1961.07 (30.3)

[a] Treatment A = coadministration of TDF and FTC to fasted subjects
[b] Treatment B = TDF/FTC CT administered to fasted subjects
[c] Median (min, max)
Data Source: Section 15, Tables 11 and 12

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

90% Confidence Interval for Geometric Mean Ratios of TDF PK Parameters for Treatment B versus Treatment A

TDF PK Parameter	Geometric Least Square Means		Geometric Mean Ratio (%)	90% Confidence Interval
	TX B[a] (N=39)	TX A[b] (N=39)		
C_{max}	240.90	256.20	94.0	85.8-103.0
AUC_{0-t}	1505.30	1505.00	100.0	94.0-106.5
AUC_{0-inf}	1854.08	1848.43	100.3	94.6-106.3

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment A = Coadministration of TDF and FTC to fasted subjects
Data Source: Section 15, Table 19

The summary statistics of FTC PK parameters are listed below.

Summary of FTC PK Parameters

FTC PK Parameter	Treatment A[a] (N=38) Arithmetic Mean (%CV)	Treatment B[b] (N=39) Arithmetic Mean (%CV)
C_{max} (μg/mL)	2.21 (26.7)	2.31 (26.0)
T_{max} (h)[c]	1.25 (0.75, 3.00)	1.50 (0.75, 3.00)
T½ (h)	15.31 (25.0)	15.64 (23.3)
AUC_{0-t} (μg·h/mL)	10.39 (20.1)	10.32 (20.6)
AUC_{0-inf} (μg·h/mL)	10.70 (20.0)	10.62 (20.2)

[a] Treatment A = coadministration of TDF and FTC to fasted subjects
[b] Treatment B = TDF/FTC CT administered to fasted subjects
[c] Median (min, max)
Data Source: Section 15, Tables 15 and 16

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

90% Confidence Interval for Geometric Mean Ratios of FTC PK Parameters for Treatment B versus Treatment A

FTC PK Parameter	Geometric Least Square Means		Geometric Mean Ratio (%)	90% Confidence Interval
	TX B[a] (N=39)	TX A[b] (N=39)		
C_{max}	2.03	2.11	96.5	89.5 -104.0
AUC_{0-t}	10.11	10.10	100.1	95.9 -104.5
AUC_{0-inf}	10.42	10.40	100.2	96.2 -104.4

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment A = Coadministration of TDF and FTC to fasted subjects
Data Source: Section 15, Table 22

Reviewer Comment: The TDF/FTC CT (TRUVADA) is BE to the TDF single tablet (VIREAD) and the FTC single capsule (EMTRIVA).

Food Effect Analysis

The summary statistics of TDF PK parameters for the food effect assessment of the study are listed below.

Food Effect on PK of TDF Administered as the TDF/FTC CT to Fasted and Fed Subjects

TDF PK Parameter	Treatment B[a] (N=39) Arithmetic Mean (%CV)	Treatment C[b] (N=39) Arithmetic Mean (%CV)	Treatment D[c] (N=39) Arithmetic Mean (%CV)
C_{max} (ng/mL)	253.63 (33.0)	293.62 (29.9)	290.17 (33.2)
T_{max} (h)[d]	0.75 (0.50, 2.50)	1.50 (0.50, 4.00)	1.50 (0.50, 4.00)
AUC_{0-t} (ng·h/mL)	1605.84 (33.3)	2246.78 (26.9)	2207.18 (26.1)
AUC_{0-inf} (ng·h/mL)	1961.07 (30.3)	2581.82 (24.9)	2561.12 (24.6)

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment C = TDF/FTC combination tablet administered with a high-fat meal
[c] Treatment D = TDF/FTC combination tablet administered with a light meal
[d] Median (min, max)
Data Source: Section 15, Tables 12, 13, and 14

The food effect GLS and 90% CI values for TDF are listed below.

Food Effect on PK of TDF Administered as the TDF/FTC CT

TDF PK Parameters	Geometric Least Square Means			TX C : TX B		TX D : TX B	
	TX B[a] (N=39)	TX C[b] (N=39)	TX D[c] (N=39)	GMR[d] (%)	90% CI	GMR[d] (%)	90% CI
C_{max}	240.90	279.52	273.36	116.0	105.9-127.1	113.5	103.6-124.3
AUC_{0-t}	1505.30	2162.02	2115.57	143.6	134.9-152.9	140.5	132.0-149.6
AUC_{0-inf}	1854.08	2499.27	2481.29	134.8	127.2-142.9	133.8	126.2-141.9

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment C = TDF/FTC combination tablet administered with a high-fat meal
[c] Treatment D = TDF/FTC combination tablet administered with a light meal
[d] GMR= Geometric Mean Ratio
Data Source: Section 15, Tables 20 and 21

Reviewer Comment: Regardless of the meal content (high-fat or light meal), a food effect does occur with TDF portion of the CT. TDF AUC_{0-inf} and C_{max} increase by approximately 35% and 15%, respectively, in a fed state as compared to TDF in a fasted state. These increases seen in AUC and C_{max} after a high-fat meal are similar to what has been reported with VIREAD (TDF single tablet). The increases in TDF exposures after a light meal differ with previous results reported with VIREAD after a light meal. The reason for these differences could be attributed to VIREAD light meal data were cross study comparisons and the TRUVADA light meal data were not. The increases in TDF concentrations are not clinically relevant because previous VIREAD safety and efficacy studies were conducted under fed conditions.

Since the approval of NDA 21-752 was based on a pivotal BE study, an inspection of the clinical trial site and the analytical laboratory site was conducted by the Division of Scientific Investigations (DSI). The pivotal BE study (GS-US-104-172) also contained the food effect analysis. Following the inspection at the clinical trial site, a Form 483 was issued for the food effect portion of GS-US-104-172. After further internal discussions, a decision was made to accept the food effect data. The basis for this decision was on the fact that the high-fat meal results from GS-US-104-172 were similar to a previous high-fat food effect study conducted with VIREAD. The excipients in TRUVADA are similar to those in VIREAD. In addition, it is not likely that a light meal would have a greater effect on exposure, compared to the high-fat meal. Thus, the current study provides an acceptable evaluation of the potential increase in TDF concentrations when administered as TRUVADA. FTC is a BCS Class 1 drug, so no food effect is expected.

Food Effect on PK of FTC Administered as the TDF/FTC CT to Fasted and Fed Subjects

FTC PK Parameter	Treatment B[a] (N=39) Arithmetic Mean (%CV)	Treatment C[b] (N=39) Arithmetic Mean (%CV)	Treatment D[c] (N=39) Arithmetic Mean (%CV)
C_{max} (µg/mL)	2.13 (28.2)	2.01 (29.4)	2.04 (28.4)
T_{max} (h)[d]	1.50 (0.75, 3.00)	1.50 (0.75, 4.07)	1.50 (0.75, 4.00)
AUC_{0-t} (µg·h/mL)	10.32 (20.6)	9.95 (20.2)	10.01 (20.3)
AUC_{0-inf} (µg·h/mL)	10.62 (20.2)	10.30 (19.8)	10.37 (20.1)

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment C = TDF/FTC combination tablet administered with a high-fat meal
[c] Treatment D = TDF/FTC combination tablet administered with a light meal
[d] Median (min, max)
Data Source: Section 15, Tables 16, 17, and 18

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

Food Effect on PK of FTC Administered as the TDF/FTC CT

FTC PK Parameters	Geometric Least Square Means			TX C : TX B		TX D : TX B	
	TX B[a] (N=39)	TX C[b] (N=39)	TX D[c] (N=39)	GMR[d] (%)	90% CI	GMR[d] (%)	90% CI
C_{max}	2.03	1.93	1.96	94.7	87.9-102.0	96.6	89.6-104.0
AUC_{0-t}	10.11	9.77	9.79	96.7	92.7-100.9	96.8	92.8-101.0
AUC_{0-inf}	10.42	10.12	10.15	97.1	93.3-101.2	97.4	93.5-101.5

[a] Treatment B = TDF/FTC combination tablet administered to fasted subjects
[b] Treatment C = TDF/FTC combination tablet administered with a high-fat meal
[c] Treatment D = TDF/FTC combination tablet administered with a light meal
[d] GMR= Geometric Mean Ratio
Data Source: Section 15, Tables 23 and 24

Reviewer Comment: No food effect exists for FTC in the TDF/FTC CT regardless of the meal contents when. These results are similar to results seen with EMTRIVA.

Assessment/Conclusion

1. TDF 300-mg/FTC 200-mg CT is BE to TDF (300-mg tablet) and FTC (200-mg capsule) administered as separate formulations in fasted subjects.
2. Regardless of the meal content (high-fat or light meal), a food effect does occur with TDF portion of the CT. TDF AUC_{0-inf} and C_{max} increase by approximately 35% and 15%, respectively, in a fed state as compared to TDF in a fasted state. These increases are not clinically significant since previous VIREAD safety and efficacy studies were conducted under fed conditions.
3. The PK of FTC was not altered by the presence of food.
4. The TDF/FTC CT can be administered with or without food.

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4.1.3 Drug Interaction Studies

Drug Interaction Study (FTC-114)

Study Objectives

Primary-

- To determine the effect of tenofovir disoproxil fumerate (TDF) on the pharmacokinetics (PK) of emtricitabine (FTC) after concurrent multiple-dose administration of therapeutically relevant doses
- To determine the effect of FTC on the PK of TDF after concurrent multiple-dose administration of therapeutically relevant doses

Secondary-

- To evaluate the safety and tolerability of repeat doses of FTC and TDF when administered alone and in combination for periods of up to 7-days

Study Design
This was an open-label, randomized, three-way crossover study conducted at a single study center, in which 19 healthy volunteers enrolled and 17 subjects completed all three dosing periods. There was no washout interval between treatments. Since TDF is recommended to be taken with food, all study medication was administered after a standard breakfast on PK assessment days. Study subjects were instructed to take medications with food on the other study days.

Treatment A: 200-mg FTC QAM x 7-days
Treatment B: 300-mg TDF QAM x 7-days
Treatment C: 200-mg FTC + 300-mg TDF QD x 7-days

Study Subjects Demographics
Of the 19 healthy volunteers enrolled, the majority (15/19) was male and all were Caucasian. The mean (range) age and weight of the subjects were 26 (19-41) years and 73.8 kg (61.7 kg - 94.4 kg), respectively. Estimated CL_{cr} values determined by using the Cockcroft Gault method and the subject's screening serum creatinine level ranged from 94 mL/min to 157 mL/min (mean 114 mL/min).

Study Drugs/Doses/Mode of Administration/Lot Numbers
- Treatment A: 200-mg FTC capsule/oral administration/Lot # TP-0006-01048/Batch Size [redacted] capsules
- Treatment B: 300-mg Viread™ tablet/oral administration/Lot # FBK013

PK Sampling Scheme
- Full PK profile evaluations were conducted on Days 7, 14, and 21 for both FTC and TDF. Blood samples for the determination of FTC and TDF concentrations were collected pre-dose and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose.
- On days 5, 6, 12, 13, 19, and 20 a single PK blood sample for analysis of $C\tau$ were collected
- Urine samples were collected prior to dosing (single void) and over the following intervals after drug administration: 0-4, 4-8, 8-12, and 12-24 hours

PK Analysis/Statistical Analysis
- Plasma FTC and TDF concentration-time profiles at steady-state were analyzed by noncompartmental methods using WinNonlin Professional version 3.3
- The following PK parameters were determined: $C_{max,ss}$, $t_{max,ss}$, $AUC\tau$, λ_z, $t½$, CL_{ss}/F, $V_{z,ss}/F$
- All PK parameters except for t_{max} were log transformed before statistical analyses. PK parameter values were compared by analysis of variance (ANOVA) using SAS PROC MIXED, version 8.1
- The criteria for a lack of clinically significant difference between the test and reference regimens were a 90% CI for the ratio of $AUC\tau$, $C_{max,ss}$ and $C_{min,ss}$ that were within the 70% to 143% range, representing a maximum of 30% difference between treatments

Reviewer Comment: The Applicant set the 90% CI range at 70-143%, which they indicate would represent a lack of clinically significant difference between the test and reference regimens. This range is an arbitrary selection. The Agency still views the appropriate 90% CI range for a lack of significant difference between the test and

reference regimens to be 80-125%. However, if the test drug falls outside this range, it may still be of no clinical significance. These decisions are made on an individual case by case basis.

Assay/Analytical Method

The methods for the determination of FTC and TDF in human plasma have been validated according to ——— applicable standard operating procedures (SOP). A liquid chromatography ———) ——— method was used to determine FTC and TDF concentrations in plasma.

Study plasma samples were analyzed with a minimum of 16 calibration standards and a minimum of 6 QC samples per analytical run. Correlation coefficients were all greater than 0.99. For FTC, inter-day precision, expressed as %CV, ranged from 4.09% to 13.86% and inter-day accuracy, expressed as %bias ranged from ——— For TDF, inter-day precision, expressed as %CV, ranged from 5.17% to 14.43% and inter-day accuracy, expressed as %bias, ranged from ——— for the human plasma assay. The lower limit of quantitation (LLOQ) of FTC for the study samples was——— and LLOQ for TDF was ———

FTC-114 Study Results

FTC

Table 1 summarizes the mean (%CV) values for FTC PK parameters when administered alone or in combination with TDF. Table 2 summarizes the statistical analysis of FTC PK parameters when administered alone or in combination with TDF.

Table 1. Mean (%CV) Values for FTC PK Parameters when Administered Alone or in Combination with TDF (N=17)

TX	Statistic	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$t_{max,ss}$ (h)	AUC_τ (µg•h/mL)	t½ (h)	CL_{ss}/F (mL/min)	V_{zss}/F (L)
FTC	Mean	1.77	0.06	3.02	10.19	10.57	340	314
	%CV	22	28	29	19	24	23	36
FTC + TDF	Mean	1.69	0.07	2.98	10.69	10.73	316	294
	%CV	18	22	20	11	16	16	20

Table 2. Statistical Analysis of FTC PK Parameters (N=17)

PK Parameter	Statistical Value	FTC (reference)	FTC + TDF (test)	Statistical Analysis	FTC +TDF / FTC
AUC_τ (µg•h/mL)	Geom. Mean	10.00	10.62	GLS Ratio 90% CI	1.065 0.997, 1.137
$C_{max,ss}$ (µg/mL)	Geom. Mean	1.73	1.67	GLS Ratio 90% CI	0.962 0.872, 1.061
$C_{min,ss}$ (µg/mL)	Geom. Mean	0.061	0.073	GLS Ratio 90% CI	1.201 1.117, 1.291

AUC_τ and $C_{max,ss}$ of FTC were not affected by TDF co-administration. Even though the FTC $C_{min,ss}$ increased by ~ 20% when co-administered with TDF, it can be concluded TDF has no clinically significant effect on the PK of FTC.

TDF Results

Table 3 summarizes the mean (%CV) values for TDF PK parameters when administered alone or in combination with FTC. Table 4 summarizes the statistical analysis of TDF PK parameters when administered alone or in combination with FTC.

Table 3. Mean (%CV) Values for TDF PK Parameters when Administered Alone or in Combination with FTC (N=17)

TX	Statistic	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$t_{max,ss}$ (h)	AUC_τ (µg•h/mL)	t½ (h)	CL_{ss}/F (mL/min)	V_{zss}/F (L)
TDF	Mean	279	54	2.43	2844	15.26	837	1128
	%CV	21	28	33	24	30	26	49
TDF + FTC	Mean	288	54	2.40	2801	15.89	829	1133
	%CV	22	20	38	18	24	18	26

Table 4. Statistical Analysis of TDF PK Parameters (N=17)

PK Parameter	Statistical Value	TDF (reference)	TDF + FTC (test)	Statistical Analysis	TDF + FTC / TDF
AUC_τ (µg•h/mL)	Geom. Mean	2768	2757	GLS Ratio	1.000
				90% CI	0.922, 1.086
$C_{max,ss}$ (µg/mL)	Geom. Mean	273	281	GLS Ratio	1.026
				90% CI	0.951, 1.106
$C_{min,ss}$ (µg/mL)	Geom. Mean	52	53	GLS Ratio	1.020
				90% CI	0.922, 1.128

FTC appears to have no effect on the PK of TDF when co-administered.

Conclusion

- TDF has no clinically significant effect on the PK of FTC when the two drugs are administered together for 7 days
- FTC has no effect on the PK of TDF when the two drugs are administered together for 7 days

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-752**	**Brand Name**	**Truvada®**
OCPB Division (I, II, III)	**DPEIII**	**Generic Name**	**Tenofovir disoproxil fumarate/emtricitabine**
Medical Division	**530**	**Drug Class**	**NRTI**
OCPB Reviewer	**Jennifer L. DiGiacinto**	**Indication(s)**	**Treatment of HIV-1 Infection**
OCPB Team Leader	**Kellie S. Reynolds**	**Dosage Form**	**Combination Tablet 300-mg tenofovir/200-mg emtricitabine**
		Dosing Regimen	**1 Tablet QD**
Date of Submission	**11March2004**	**Route of Administration**	**PO**
Estimated Due Date of OCPB Review	**July 30, 2004**	**Sponsor**	**Gilead**
PDUFA Due Date	**11SEPT2004**	**Priority Classification**	**1P**
Division Due Date	**July 15, 2004**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			GS-US-104-172
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			GS-US-104-172
fasting / non-fasting multiple dose:				GS-US-104-172
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x			FTC-114
In-vivo effects of primary drug:	x			FTC-114
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			GS-US-104-172
replicate design; single / multi dose:				
Food-drug interaction studies:	**x**			GS-US-104-172
Dissolution:	**x**			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	2			

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**x**	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD).

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/s/

Jennifer DiGiacinto
7/29/04 04:08:10 PM
BIOPHARMACEUTICS

Kellie Reynolds
7/29/04 04:57:47 PM
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