CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-500

Clinical Pharmacology and Biopharmaceutics Review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21500	Submission Date(s): September 03, 2002, February 28, 2003, April 4, 2003, April 16, 2003, April 18, 2003, April 28, 2003, April 29, 2003, May 15, 2003, May 21, 2003, June 2, 2003, June 3, 2003, June 10, 2003, June 18, 2003, and June 20, 2003
Brand Name	EMTRIVA®
Generic Name	Emtricitabine
Reviewer	Jennifer L. DiGiacinto, Pharm.D.
Team Leader	Kellie Reynolds, Pharm.D.
PM Reviewer	Jenny J. Zheng, Ph.D.
OCPB Division	DPE III
OND Division	DAVDP
Applicant	Gilead
Relevant IND(s)	IND [redacted]
Submission Type; Code	Standard (1S)
Formulation; Strength(s)	200 mg capsule
Indication	Treatment of HIV infection in combination with other antiretroviral drugs

1. EXECUTIVE SUMMARY

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor (NRTI), which is proposed for the treatment of HIV infection in adults at least 18 years of age. FTC 200 mg once daily was studied in treatment-naïve and treatment-experienced subjects. In support of this NDA, the Applicant adequately addressed the following issues:

- Basic pharmacokinetic characteristics of FTC
- Appropriate dosing adjustments for patients with renal impairment
- Low potential for metabolism based drug interactions
- No significant drug interaction with several renally eliminated drugs
- Clinical trial materials are BE to the to-be-marketed FTC

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

- Submit the final study report for study TPI DOC #15396 within one month of the date of this letter. This study evaluates the enzymes that metabolize emtricitabine.
- Please identify the enzymes responsible for emtricitabine metabolism.
- Please determine the potential for enzyme inducers to decrease emtricitabine plasma concentrations.

2. TABLE OF CONTENTS

3. SUMMARY OF CLINICAL PHARMACOLOLGY & BIOPHARMACEUTICS FINDINGS

Emtricitabine (FTC) is a synthetic deoxycytidine nucleoside analog. FTC exhibits anti-HIV-1 activity with a mean *in vitro* 50% inhibitory concentration (IC_{50}) and 90% inhibitory concentration (IC_{90}) of 0.008 and 0.055 μM (or 0.002 and 0.014 μg/mL), respectively, in clinical isolates. The Ki (affinity constant) of FTC-5'-triphosphate (FTC-TP) for the HIV Reverse Transcriptase (HIV-RT) is 0.60 μM. The steady state FTC C_{min} concentration following a 200-mg once daily dose averaged ~ 0.075 μg/mL, which is approximately 5-fold higher than the mean *in vitro* IC_{90} value (0.014 μg/mL). In the pivotal bioequivalence (BE) study, Study FTC-111, FTC 200-mg to-be-marketed capsule formulation was BE to the 100-mg capsules used in the Phase I, II studies and the pivotal Phase III safety and efficacy studies. The clinical pharmacology and pharmacokinetic profile of FTC has been defined in both healthy and HIV-infected subjects. These studies show FTC has the following clinical pharmacology characteristics.

- FTC plasma concentrations are measurable at the earliest sampling time (15 minutes post dose) and reach C_{max} within 1-2 hours
- FTC absolute bioavailability (F) value is 93%
- FTC disposition follows linear, first-order kinetics. Steady state plasma FTC concentration-time profiles are predictable based on single dose data.
- C_{max} value (~ 2 μg/mL) did not show substantial increase following multiple-dose administration, indicative of minimal accumulation
- The steady state AUC over a 24-hour dosing interval following a 200-mg once daily dose averaged 10 μg•h/mL, which is the same as the $AUC_{0-\infty}$ value after single-dose administration
- FTC steady state was achieved following 4 once daily doses
- Protein binding studies conducted over a wide concentration (0.02-200μg/mL) range revealed that < 4% of FTC is bound to human plasma proteins
- At peak plasma concentration, the mean FTC plasma to blood drug concentration ratio was ~ 1.0 and the mean FTC semen to plasma drug concentration ratio was ~ 4.0
- FTC is primarily eliminated from plasma as unchanged FTC in urine (about 60-70% of an oral dose), with an elimination half-life of 9-10 hours
- *In vitro* studies indicate that FTC is not an inhibitor of human CYP450 enzymes
- The renal clearance of FTC is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion
- As compared to fasted conditions, a high-fat meal reduces the FTC absorption rate (as evidenced by a 1.5-hour increase in t_{max}. Additionally, FTC C_{max} was decreased by 29% after a high-fat meal and AUC did not change. Based on clinical trial experience with FTC and experience with other NRTIs, FTC can be administered with or without food.
- FTC pharmacokinetics are similar between healthy and HIV-infected subjects
- There are no FTC pharmacokinetic differences between female and male subjects
- FTC shows low inter-subject variability in its pharmacokinetic parameter estimates
- The pharmacokinetics of FTC are altered in patients with renal impairment. It is recommended that the dosing interval for FTC be increased in patients with creatinine clearance < 50 mL/min and in patients with ESRD who require dialysis.

- The applicant has not appropriately identified the enzymes responsible for FTC metabolism. Even though metabolism is a minor pathway (~13%), a minor pathway can become a major pathway if inhibited. The applicant has agreed to study the metabolism of FTC as a Phase IV commitment. In addition, the applicant has agreed to determine the potential for enzyme inducers to decrease emtricitabine plasma concentrations.
- The applicant studied drug-drug interactions between FTC and other compounds that are eliminated by active tubular secretion and a CYP3A4 substrate. See these results in the tables below.

Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Co-administered Drug[1]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Stavudine	40 x 1	200 x 1	6	⇔	⇔	-
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-

1. All interaction studies conducted in healthy volunteers
2. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Emtricitabine[1]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Stavudine	40 x 1	200 x 1	6	⇔	⇔	-
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-

1. All interaction studies conducted in healthy volunteers
2. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

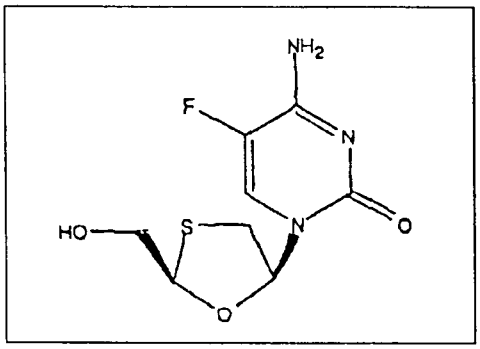
4. Question Based Review

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The structure and physical properties of FTC are shown below:

Structural Formula: $C_8H_{10}FN_3O_3S$



Chemical Name: 5-fluoro-1-[(2R, 5S-2-hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
Molecular Weight: 247.24
Solubility in H_2O: 112-mg/mL
pH-solubility profile:

- pH 4.0 - 61.6-mg/mL
- pH 6.0 - 61.3-mg/mL

pKa Value: 2.65 ± 0.01
Octanol/H_2O Partition Coefficient: Log P value -0.43
UV Absorbance:

The quantitative composition of the to-be-marketed FTC capsules is shown in the following table:

	Function	200-mg Capsule Quantity (mg/capsule)
Active Ingredient:		
Emtricitabine	Active	200.0
Inactive Ingredients:		
Microcrystalline Cellulose, NF		
Crospovidone, NF		
Povidone, NF		
Magnesium Stearate, NF		
Total Fill Weight:		400.0
Capsule/Shell (Size 1)		1 each

4.1.2 What is the proposed mechanism of drug action and therapeutic indication?

FTC is a synthetic nucleoside analog of cytosine. FTC is phosphorylated by cellular enzymes to form FTC- 5'-triphosphate, which inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate. Emtricitabine 5'-triphosphate is incorporated into proviral DNA and results in chain termination.

4.1.3 What is the proposed dosage and route of administration?

The dose of FTC is 200 mg once daily taken orally with or without food in patients 18 years and older. The label also recommends dose modifications for patients with renal impairment.

Patients with Renal Impairment:

Dosing Interval Adjustment in Patients with Renal Impairment

	Creatinine Clearance (mL/min)			
Recommended Dose and Dosing Interval	≥ 50 mL/min	30 - 49 mL/min	15 - 29 mL/min	< 15 mL/min (including patients requiring hemodialysis)
200-mg	every 24 hours	every 48 hours	every 72 hours	every 96 hours

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

4.1.4 What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data?

Two pivotal Phase III studies (FTC-301A and FTC-303) provide safety and efficacy data.

Study FTC-301A:
This was a Phase III, 48-week, double-blind, active-controlled multi-center study designed to compare FTC (200-mg QD) administered in combination with didanosine (ddI) and efavirenz (EFV) versus stavudine (d4T), ddI, and EFV in 571 antiretroviral naïve patients. The antiviral efficacy of the FTC 200-mg QD treatment arm was statistically significantly higher compared to the active-control arm for proportion of subjects responding to treatment with HIV-RNA ≤ 50 copies/mL through 48 weeks of treatment (73% FTC; 56% d4T).

Study FTC-303:
This was a 48-week, open-label, active-controlled multi-center study comparing FTC to 3TC, in combination with d4T or ZDV and a protease inhibitor or NNRTI in 440 patients who were on 3TC-containing antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-RNA ≤ 400 copies/mL. The antiviral efficacy of the FTC 200-mg

QD treatment arm was similar to the 3TC containing treatment arm for proportion of subjects responding to treatment with HIV-RNA < 400 copies/mL through 48 weeks of treatment (73% FTC; 82% 3TC).

Safety:
The most common adverse events that occurred in patients receiving FTC with other antiretroviral agents in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. With the exception of skin discoloration, which was reported with higher frequency in the FTC treated group, all other adverse events were reported with similar frequency in FTC and control treatment groups. Skin discoloration was predominantly observed in Black patients.

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The surrogate efficacy endpoints for HIV-1 infection are plasma HIV viral load (HIV-RNA) and CD4 cell counts. The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for FTC-303 was the percent of patients with HIV-RNA $\leq$ 400 copies/mL analyzed by the Intention-to - Treat (Non-Complete = Failure). At the request of the FDA, a Time to Loss of Virologic Response (TLOVR) algorithm was also used to analyze the data for FTC-303.

The primary efficacy endpoint for the second pivotal study (FTC-301A) was the percent of patients with HIV-RNA $\leq$ 50 copies/mL analyzed by the Intention-to-Treat (Non-Complete = Failure). Additionally, a TLOVR algorithm was used to analyze the data for FTC-301A.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

FTC concentrations in human plasma and human urine samples were determined by validated [redacted] methods using [redacted] plasma and [redacted] urine samples or dilution of the urine followed by direct injection onto [redacted] The assays are acceptable. See section 4.6 for further details. No active metabolites are present in the plasma; however, the active FTC intracellular metabolite is FTC-5'-TP.

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

See 4.2.3.3

4.2.3.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

FTC PK Parameter Estimates (Arithmetic Mean, %CV) Following Single Dose Administration (Day 1) by Dose Cohort and Dose (Study FTC-101, HIV-Infected)

TX	Statistic	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-t} (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	Estimated t½ (h)	CL/F (mL/min)
25-mg BID (n = 9)	Mean	0.15	1.60	0.60	0.68	3.61	638
	%CV	24	53	21	21	21	22
100-mg BID (n = 8)	Mean	0.90	2.41	3.68	4.14	3.26	440
	%CV	37	52	27	35	23	29
200-mg BID (n = 8)	Mean	1.63	1.14	5.99	6.37	2.83	535
	%CV	21	34	16	16	10	15
100-mg QD (n = 8)	Mean	0.98	1.54	3.16	3.42	3.48	537
	%CV	43	45	33	32	24	35
200-mg QD (n = 8)	Mean	1.54	2.25	6.47	7.07	2.98	489
	%CV	38	46	18	19	14	22
100-mg combined (n = 16)	Mean	0.94	1.97	3.42	3.78	3.37	489
	%CV	40	55	30	34	23	34
200-mg combined (n = 16)	Mean	1.59	1.70	6.23	6.72	2.90	512
	%CV	30	56	17	18	12	18

FTC PK Parameter Estimates (Arithmetic Mean, %CV) at Steady-State (Day 10) by Dose Cohort/Dose Regimen

TX	Statistic	$C_{max,ss}$ (μg/mL)	$t_{max,ss}$ (h)	$C_{min,ss}$ (μg/mL)	AUC_{τ} (μg·h/mL)	t½ (h)	CL_{ss}/F (mL/min)
25-mg BID (n = 9)	Mean	0.23	1.39	0.029	0.99	5.26	430
	%CV	30	39	32	17	8	17
100-mg BID (n = 8)	Mean	1.15	1.69	0.148	5.39	4.25	339
	%CV	19	63	68	35	15	30
200-mg BID (n = 8)	Mean	2.05	1.23	0.171	8.47	3.59	415
	%CV	34	28	23	26	16	26
100-mg QD (n = 8)	Mean	0.90	1.21	0.035	4.10	9.49	423
	%CV	20	23	50	22	21	21
200-mg QD (n = 8)	Mean	1.72	2.00	0.047	8.00	8.24	425
	%CV	53	48	24	15	31	15

FTC demonstrates linear pharmacokinetics over the dose range studied and steady-state concentrations were predictable based on single dose data. Both FTC QD regimens had longer half-life values when compared to the BID regimens. This was seen in earlier PK studies and is related to duration of FTC sampling collection for the different FTC regimens. The applicant notes that large differences in the t½ can be explained by the difference in collecting samples 12 hours versus 24 hours post-dose administration. The 9-10 hour t½ is a more accurate half-life for FTC based on when steady state levels are achieved. Based on the Cτ values, the applicant reports FTC reaches steady state after 4 days of FTC administration.

4.2.3.2 Do PK parameters change with time following chronic dosing?

FTC-303 sub-study was designed to confirm the PK profile of FTC at steady-state when administered to HIV-1 infected subjects (measured between Week 4 to Week 38). The table below summarizes the FTC PK parameter estimates determined at steady state.

Descriptive Statistics for FTC PK Parameter Estimates Determined at Steady-State (FTC-303 Sub-study, N = 12)

Dose Regimen	Statistic	$C_{max,ss}$ (μg/mL)	$t_{max,ss}$ (h)	$C_{min,ss}$ (μg/mL)	AUC_{τ} (μg·h/mL)	t½ (h)	CL_{ss}/F (mL/min)
200-mg QD	Mean	1.94	1.80	0.11	11.31	8.08	317
	%CV	(24)	(58)	(71)	(29)	(32)	(27)

FTC-303 data indicate FTC pharmacokinetic parameter values are consistent with previous PK study data (Following multiple dose oral administration of FTC to 20 HIV-infected subjects, the (mean ± SD) steady-state plasma FTC C_{max} was 1.8 ± 0.7 mg/mL and the AUC_{24} was 10.0 ± 3.1 hr•mg/mL). No changes are evident with chronic FTC dosing when compared to single-dose or short term multiple dosing.

4.2.3.3 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

In Study FTC-101 the safety, tolerability, pharmacokinetics, and antiviral activity of different dosing regimens of FTC monotherapy in HIV-infected subjects were investigated. The FTC doses studied in FTC-101 included 25-mg BID, 100-mg QD and BID, and 200-mg QD and BID. The table below summarizes the median change from baseline in Log_{10} HIV-1 RNA over time by dosing cohort.

Median Change from Baseline in Log_{10} HIV-1 RNA Over Time by Cohort

Time	FTC 25-mg BID N=7	FTC 100-mg QD N=8	FTC 100-mg BID N=8	FTC 200-mg QD N=8	FTC 200-mg BID N=7	All Cohorts N=38
Baseline Viral Load	4.3	4.5	4.4	4.6	4.8	4.6
Day 1	0.1	-0.1	0.0	-0.1	0.0	0.0
Day 3	-0.2	-0.5	-0.5	-0.6	-0.4	-0.5
Day 5	-1.0	-1.0	-1.1	-1.0	-1.1	-1.0
Day 8	-1.4	-1.4	-1.5	-1.5	-1.7	-1.5
Day 12	-1.5	-1.4	-1.7	-1.7	-1.9	-1.6
Day 15	-1.3	-1.5	-1.7	-1.9	-1.9	-1.6

All doses of FTC produced antiviral activity. There was a trend for less antiviral activity at doses of 50 to 100-mg of FTC per day as compared to ≥ 200-mg of FTC per day. Since no clear increase in antiviral activity was seen after doubling the FTC dose from 200-mg QD to 200-mg BID, the 200-mg QD dosing regimen was selected as the dose to go forward in the Phase III studies. No further dose finding studies were conducted during Phase II development.

The most common adverse events (ADEs) reported were asthenia (34.1%), nausea (31.4%), headache (22.0%), pharyngitis (19.5%), and rhinitis (19.5%). Most ADEs were mild, few were moderate or severe and none life threatening. A dose-response relationship was not evident with respect to frequency or severity of ADEs.

4.2.4 How does the PK of FTC in healthy volunteers compare to those in patients?

4.2.4.1 What are the basic PK parameters?

The pharmacokinetics of emtricitabine were evaluated in healthy volunteers and HIV-infected individuals. Emtricitabine pharmacokinetics are similar between these populations. See table below.

Basic Pharmacokinetic Parameters Comparison of FTC in Healthy Volunteers and HIV-1 Infected Subjects, Mean (%CV) [FTC Dose = 200-mg QD]

Study	N	$C_{max,ss}$ (μg/mL)	$t_{max,ss}$ (h)	$C_{min,ss}$ (μg/mL)	AUCτ (μg•h/mL)	t½ (h)	CL_{ss}/F (mL/min)
FTC-303 HIV-infected	12	1.94 (24)	1.80 (58)	0.11 (71)	11.31 (29)	8.08 (32)	317 (27)
FTC-101 HIV-infected	8	1.72 (53)	2.00 (48)	0.047 (24)	8.00 (15)	8.24 (31)	425 (15)
FTC-114 Healthy Subjects	17	1.77 (22)	3.02 (29)	0.06 (28)	10.19 (19)	10.57 (24)	340 (36)

The absolute BA for FTC is 93%. FTC is predominantly eliminated from the plasma as unchanged FTC in the urine. The renal clearance (CL_R) of emtricitabine is greater than the estimated creatinine clearance (CL_{cr}), suggesting elimination by both glomerular filtration and active tubular secretion.

4.2.4.2 Does mass balance study suggest the major route of elimination is renal or hepatic?

The mass balance study in humans (n = 5) showed that the overall recovery of ^{14}C-radioactivity dose was almost complete; > 99% dose recovered in urine and feces. Complete recovery of a single ^{14}C-FTC dose in urine (approximately 86%) and feces (approximately 14%) occurs within seven days. FTC is predominantly eliminated from the plasma as unchanged FTC in the urine (60-70%). Metabolism is a minor elimination pathway for FTC; only 13% of the dose was recovered in urine as 3 putative metabolites. FTC metabolites are formed by an oxidation of the thiol moiety to form 3'-sulfoxide diastereomers (designated M1 and M2) and conjugation with glucuronic acid to form the 2'-O-glucuronide (designated M3).

4.2.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In general, FTC pharmacokinetic parameter estimates following oral administration are characterized by low inter-subject and low intra-subject variability. Consistent pharmacokinetic data have been observed between healthy volunteers and HIV-1 infected subjects.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

The applicant evaluated the effect intrinsic factors (gender, race, and renal impairment) has on the PK of FTC, as described below. A dosage regimen adjustment is needed for patients with renal impairment.

4.3.1.2 Renal Impairment

Based on the pharmacokinetic characteristics of FTC determined in the clinical studies, renal function, as reflected by the estimated creatinine clearance, is the most important factor affecting the pharmacokinetics of FTC because:

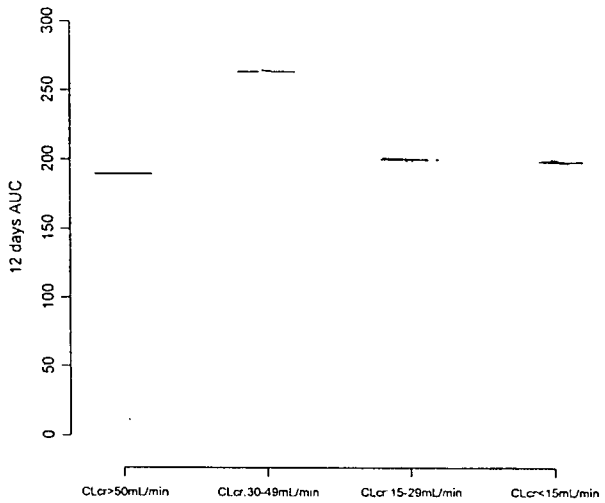
- FTC is rapidly and extensively absorbed orally with little or no first-pass metabolism and high (93%) oral bioavailability
- FTC shows low inter-subject variability in its pharmacokinetic parameter estimates
- FTC is primarily eliminated via renal excretion (60 -70% of an oral dose) with metabolism as the minor elimination pathway (< 13% of an oral dose)

One study in special populations, i.e., adults with renal impairment FTC-107, indicates there is a statistically significant linear relationship between the CL/F values of FTC and the estimated creatinine clearance (CL_{cr}). Based on the pharmacokinetic results of Study FTC-107 in subjects with varying degrees of renal impairment, dosage adjustment for FTC has been proposed by the Applicant for patients with renal impairment. Since FTC will be commercially marketed in only a 200-mg capsule formulation, dosing adjustments will be achieved by extending the dosing interval. See table below.

Creatinine Clearance	200 mg emtricitabine
≥ 50mL/min	Q24h
30-49 mL/min	Q48h
15-29 mL/min	Q72h
<15mL/min including patients requiring hemo-dialysis	Q96h

Dr. Jenny J. Zheng conducted additional modeling and simulation with the differing FTC dosing intervals. This analysis provides the predicted FTC exposures for each of the proposed dosing intervals. These results are listed below. She compared two parameters, simulated AUC (cumulative over 12 days) and the simulated trough concentration (C_τ) at steady state between groups based on the proposed dose regimens. The simulated AUC (over 12 days) for each subject and each group according to the CLcr are shown in the Figure 1 below. The circles represent the individual data and the line is the median value in the group.

Figure 1. FTC Simulated AUC_{ss} (over Days 1-12) for Groups with Varying Degree of Renal Impairment



The steady state trough concentrations are obtained from simulation. The pharmacokinetic model was obtained from fitting the concentration versus time data after a single dose. It was found that the 2-compartment model with first order delayed absorption and first order elimination can best describe the data. The estimated pharmacokinetic parameters were used to simulate the concentration time profiles at steady state.

The profiles and trough concentrations from the simulation are shown in the Figures 2 and 3 below.

Figure 2. Simulated FTC Cτ,ss Profiles for Varying Degrees of Renal Impairment

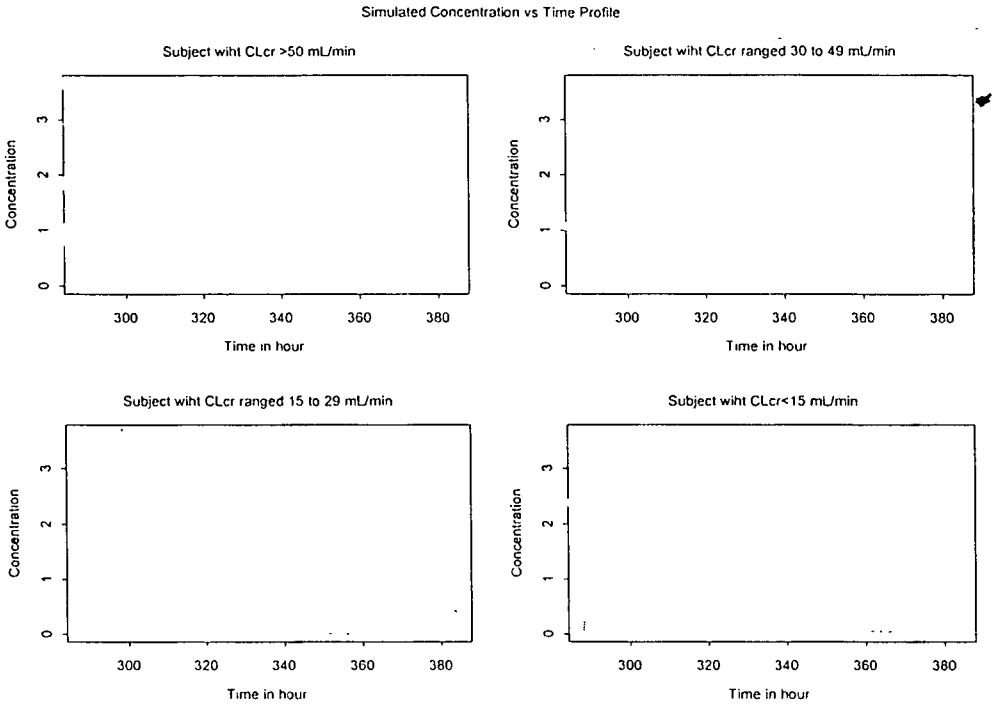


Figure 3. Simulated FTC $C_{\tau,ss}$ Values for Varying Degrees of Renal Impairment

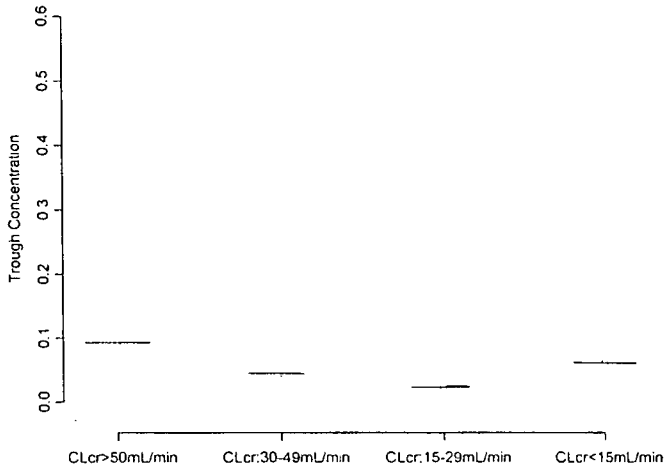


Figure 2 shows the simulated steady state maximal concentration ($C_{max,ss}$) in subjects with CLcr< 29 mL/min are somewhat lower than the $C_{max,ss}$ in the subjects with CLcr $\geq$ 30 mL/min.

Figure 3 shows the simulated steady state trough concentrations ($C\tau_{,ss}$) in each dosing group. The median $C\tau_{,ss}$ are 0.0933, 0.04455, 0.0225, and 0.0604 mg/mL in subjects with CL_{cr} >50mL/min, CL_{cr} range 30-49 mL/min, CL_{cr} range 15-29 mL/min, and CL_{cr} <15mL/min, respectively. The $C\tau_{,ss}$ in subjects with CL_{cr} >80 mL is 0.0836 mg/mL. The results show that $C\tau_{,ss}$ in subjects with CLcr < 49 mL/min are lower as compared with $C\tau_{,ss}$ in subjects who take the drug q24h. However, the $C\tau$ values for all groups are above the IC_{50} and IC_{90} values 0.002 and 0.014 µg/mL. Since the active moiety of drugs in the nucleoside reverse transcriptase class (NRTI) is the intracellular tri-phosphorylated moiety, reaching $C\tau$ values > IC_{90} for drugs in this class is not as critical as compared to protease inhibitor class or non-nucleoside reverse transcriptase class.

It appears the achieved FTC AUC and $C_{\tau,ss}$ values for subjects with varying degrees of renal impairment are acceptable with the proposed dose reduction.

4.3.1.3 Age and gender

Demographic factors/variables affecting the estimation of CL_{cr}, such as body weight, gender, and age, are expected to contribute to the variations in FTC pharmacokinetics among different populations. To explore this hypothesis, the Applicant used regression analysis (simple regression and stepwise multiple regression) along with analysis of variance (ANOVA) to evaluate the relationship of one or more independent demographic variables (age, weight, body surface area, gender, race, and CL_{cr}) to a single dependent variable, e.g., AUC and other key pharmacokinetic variables. The analysis results confirmed that CL_{cr} is the most important variable affecting the overall plasma exposure of FTC. Age, gender, and body weight were secondarily important in influencing AUC

and half-life estimates due to their effect on CL_{cr} and consequently total body clearance. No specific gender studies were conducted to address whether there are differences in FTC PK between male and female subjects. Additionally, no study was conducted to address dosing in the geriatric population, but because renal function tends to decline with age, dosing adjustment may be warranted for elderly patients with lower CL_{cr}.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Refer to Drug-Drug Interactions section (Section 4.4.2) for the potential effects of other drugs on FTC and of FTC on other drugs. Refer to Section 4.5.3 for food effect.

4.4.2 *Drug-Drug Interactions*

4.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

An *in vitro* study was conducted to evaluate the potential for FTC to inhibit human cytochrome P450 (CYP) 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4/5 activities and UGT as determined with probe substrates. At concentrations up to 14-fold higher than those observed in vivo, FTC did not inhibit any of the CYP enzymes listed above. Based on these results and the known renal elimination pathways of FTC, the potential for CYP450 mediated interactions involving FTC with other drug products is low.

4.4.2.2 Are there other metabolic/transporter pathways that may be important?

The primary route of FTC elimination is by renal excretion. In humans, the renal clearance (CL_R) is $\geq$ 200 mL/min. This high CL_R value, relative to CL_{cr}, indicates that FTC undergoes glomerular filtration as well as active renal tubular secretion. Therefore, drugs that are secreted via the same renal tubular transporter could compete with FTC. If this would occur, the clearance of either drug or both drugs could be decreased. Clinical studies were conducted to evaluate the potential for a pharmacokinetic drug interaction between drugs that are eliminated via active tubular secretion.

4.4.2.3 What interaction data are available? What is the impact?

FTC has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (TDF), indinavir (IDV), famciclovir (FCV), stavudine (d4T), and zidovudine (ZDV). See the drug-drug interactions tables below for a summary of these study results.

Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Co-administered Drug[1]

Co-Administer-ed Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
d4T	40 x 1	200 x 1	6	⇔	⇔	-
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-

3. All interaction studies conducted in healthy volunteers
4. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Emtricitabine[1]

Co-Administer-ed Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
d4T	40 x 1	200 x 1	6	⇔	⇔	-
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-

3. All interaction studies conducted in healthy volunteers
4. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

4.4.2.4 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

The applicant has not appropriately identified the enzymes responsible for FTC metabolism. Even though metabolism is a minor pathway (~13%), a minor pathway can become a major pathway if inhibited. The applicant has agreed to study the metabolism of FTC as a Phase IV commitment. In addition, the applicant has agreed to determine the potential for enzyme inducers to decrease emtricitabine plasma concentrations.

4.5 General Biopharmaceutics

4.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Two bioequivalence (BE) studies (FTC-109 and FTC-111) were performed to compare the bioavailability (BA) of FTC between the 100-mg capsule formulation used in early Phase I clinical studies and pivotal efficacy studies and the BA of the proposed commercial FTC 200-mg capsule formulation.

A pilot study, FTC-109, conducted in 12 healthy volunteers, demonstrated that the geometric least-squares (GLS) mean ratio (one 200-mg FTC capsule vs. two 100-mg FTC capsules) for $AUC_{0-\infty}$ was 0.97 (90% CI 0.89-1.06) and the GLS mean ratio for C_{max} was 0.98 (90% CI: 0.83-1.15). These results provided the required variability data needed to determine sample size for the definitive BE study.

FTC-111 is the pivotal study that assessed the BE of the 200-mg capsule formulation intended for marketing compared to the 100-mg capsule that was used in pivotal clinical studies. Additionally, FTC-111 investigated the effect of food (standard high-fat meal) on the BA of FTC.

The summary statistics of FTC pharmacokinetic parameters are listed in the Table below.

FTC Arithmetic Mean (%CV) Pharmacokinetic Arithmetic Values

TX (n)	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0\text{-last}}$ (µg·h/mL)	$AUC_{0\text{-inf}}$ (µg·h/mL)	Estimated t½ (h)	CL/F mL/min	V_z/F (L)
2 x 100-mg cap N=24	Mean (%CV)	1.890 (29)	1.33 (32)	9.12 (22)	9.50 (21)	6.17 (15)	365 (20)	198 (30)
200-mg cap N=24	Mean (%CV)	2.010 (26)	1.08 (27)	9.32 (22)	9.66 (21)	5.89 (18)	359 (20)	186 (32)
200-mg cap/fed N=24	Mean (%CV)	1.422 (17)	2.57 (27)	8.38 (16)	8.69 (16)	5.54 (7)	393 (15)	189 (18)

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

Statistical Analysis of FTC Pharmacokinetic Parameters

Statistic	GLS Mean 100-mg (x2)	GLS Mean 200-mg	GLS Mean 200-mg/fed	GLS Ratio B/A (90% CI)	GLS Ratio C/B (90% CI)
$AUC_{0\text{-inf}}$ (μg·h/mL)	9.31	9.46	8.59	1.017 (0.972-1.064)	0.908 (0.867-0.950)
$AUC_{0\text{-last}}$ (μg·h/mL)	8.92	9.11	8.28	1.021 (0.973-1.072)	0.909 (0.866-0.954)
C_{max} μg/mL	1.81	1.95	1.40	1.073 (0.991-1.162)	0.720 (0.665-0.780)

FTC-111 data demonstrate the 200-mg capsule (to-be marketed formulation) is BE to the 100-mg capsule.

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

Study FTC-111 investigated whether or not there was a food effect with FTC administration. When FTC is administered after the ingestion of a standard high-fat meal, the rate of absorption is decreased, which is reflected in the 1.5-hour increase in Tmax. FTC's C_{max} decreased significantly (29%) after a high-fat meal; however, the overall FTC exposure ($AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$) was not significantly different. NRTIs, as a class of drugs, are dependent on the intracellular concentration of drug for activity. In theory the total exposure (AUC) is a better indicator for FTC intracellular concentrations versus C_{max}. Therefore, these differences do not appear to be of clinical significance. It is safe to conclude FTC can be administered with or without respect to food. Clinical trials for FTC were conducted without regard to food.

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

The proposed dissolution method for COVIRACIL™ 200-mg capsule is as follows:

Apparatus USP 2 (paddle)
Rotation Speed 50 rpm
Temperature: 37.5° C ± 0.5° C
Medium Tier 1: 900 mL of 0.1 N HCl
Medium Tier 2: 900 mL of 0.1 N HCl containing ≤ 750 000 USP units/L pepsin
Sampling Time: 30 minutes
Sample Amount: One capsule per vessel
Filter:
Sample Volume: 10 mL
Analytical Method:

The proposed dissolution specification for COVIRACIL™ 200-mg capsules is Q = [redacted]% dissolved in 30 minutes.

The proposed dissolution method and specification are acceptable.

4.5.4 What is the basis of the approval for all strengths of FTC capsules?

There is one strength of FTC, 200-mg capsule.

4.5.5 *If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated?*

The Applicant conducted two supportive BE studies, FTC-112 and FTC-113. The primary objective for FTC-112 was to evaluate whether the encapsulation of 3TC tablets purchased from a commercial source in South Africa for use in the Phase III Study FTC-302 affected the oral bioavailability of 3TC. The primary objective of FTC-113 was to ensure that the over-encapsulation of d4T capsules purchased from a commercial source for use in the Phase III Study FTC-301 did not affect the oral bioavailability of d4T. The study results for both FTC-112 and FTC-113 are listed in the tables below.

Study FTC-112 Descriptive Statistics for 3TC PK Parameters by Treatment

Treatment	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{½}$ (h)	CL/F (mL/min)
EPIVIR™ US^ (N=26)	Mean %CV	1.70 23	0.88 35	7.00 14	6.32 7	364 14
EPIVIR™ SA* (N=25)	Mean %CV	1.79 23	0.86 36	7.07 15	6.35 14	362 16
Encapsulated EPIVIR™ SA* (N=25)	Mean %CV	1.91 22	0.94 27	7.02 14	6.37 10	363 14

* SA-South Africa
^ US- United States

Study FTC-112 Statistical Analysis Results of 3TC $AUC_{0-\infty}$ and C_{max} Values

Statistic	Treatment Comparison		
	SA/US	Encapsulated SA/SA	Encapsulated SA/US
$AUC_{0-\infty}$ (µg•h/mL) **GLS Mean Ratio** **90% CI**	1.01 0.98, 1.05	0.99 0.95, 1.03	1.00 0.97, 1.04
C_{max} (µg/mL) **GLS Mean Ratio** **90% CI**	1.06 0.98, 1.14	1.05 0.97, 1.13	1.11 1.03, 1.20

The PK parameter estimates are similar for the three tablet formulations. The 3TC encapsulated SA formulation is BE to the 3TC SA and 3TC US formulation. The SA formulation is BE to the US formulation.

Study FTC-113 Descriptive Statistics for d4T PK Parameters by Treatment

Treatment	Statistic	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-t} (μg•h/mL)	$AUC_{0-\infty}$ (μg•h/mL)	t½ (h)
Zerit™ (40-mg capsule) (N=18)	Mean %CV	0.834 24	0.81 33	2.05 14	2.11 14	1.74 15
Zerit™ (over-encapsulated, 40-mg) (N=18)	Mean %CV	0.766 18	0.92 40	2.03 14	2.09 14	1.78 16

Study FTC-113 Statistical Analysis Results of d4T $AUC_{0-\infty}$ and C_{max} Values

PK Parameter	Statistical Value	d4T (reference)	d4T (encapsulated) (test)	Statistical Analysis	d4T-encapsulated d4T
$AUC_{0-\infty}$ (μg•h/mL)	Geom. Mean	2.09	2.07	GLS Ratio 90% CI	0.988 0.943, 1.035
C_{max} (μg/mL)	Geom. Mean	0.81	0.75	GLS Ratio 90% CI	0.924 0.831, 1.028

The over-encapsulated 40-mg Zerit™ capsules used in the pivotal Phase III efficacy study, FTC-301, are BE to the commercial 40-mg Zerit™ capsules.

4.6 Analytical Section

4.6.1 Which moieties have been selected for analysis and why?

FTC was selected for analysis, because it is the only active moiety circulating in the plasma after FTC administration.

4.6.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total FTC concentration was measured. FTC is not highly bound. In fact < 4% is bound drug, thus measuring free FTC versus total FTC will not be much different.

4.6.3 What bioanalytical methods are used to assess concentrations?

The following table provides a summary of the *in vitro* analytical methods used for the determination of plasma concentrations of FTC and other drugs in each study.

Analyte	Methods	Study	MQL[a] (ng/ml)	Linear range (ng/ml)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)
FTC Plasma Urine	\	143-001	80-ng/mL 1 μg/mL	\	Na^ Na^	Na^ Na^	Na^ Na^
FTC Plasma	\	FTC-101	5-mg/mL	\	6.85 - 9.8	-1.3 - 2.0	5, 25, 1000,

FTC Urine			250-ng/mL				4000-ng/mL
FTC Plasma		FTC-103	10-ng/mL		4.77- 12.12	-2.0 - 4.8	10.1, 202, 505, 1010, 3535-ng/mL
ZDV Plasma			10-ng/mL		6.77- 10.28	-6.2 - 4.4	9.9, 198.4, 496, 992, 3472-ng/mL
d4T Plasma			50-ng/mL		6.69 - 13.09	-1.6 - 6.7	49.7, 198.8, 497, 994, 3479-ng/mL
FTC Plasma		FTC-104	10-ng/mL		6.17 - 9.55	-7.3 - 4.0	10, 100, 500, 1000, 2500-ng/mL
IDV Plasma			20-ng/mL		5.37 - 10.09	0.5 - 7.1	20, 1000, 4000, 10000-ng/mL
FTC Plasma		FTC-106	5-ng/mL		2.09 - 12.11	-2.0 - 6.4	5, 25, 1000, 4000-ng/mL
FTC Urine			2.5-µg/mL		1.84 - 5.56	-9.1 - 8.0	
FTC Semen			5-ng/mL		----------	----------	
FTC Plasma		FTC-107	5-ng/mL		6.3 -7.3	1.0 - 9.4	5, 25, 1000, 4000-ng/mL
FTC Urine			2.5-µg/mL		5.5 - 10.1	-2.4 - 6.8	
FTC Dialysate			5-ng/mL		6.3 - 7.3	1.0 - 9.4	5, 25, 1000, 4000-ng/mL
FT C Plasma		FTC-108	25-ng/mL		8.00 - 17.56	-1.0 - 4.0	5, 25, 1000, 4000-ng/mL
FTC Urine			2.5-µg/mL		5.55 - 9.86	2.7 - 8.0	
PCV Plasma		FTC-108	25-ng/mL		8.51- 14.06	7.5 -6.5	
PCV Urine			2.5-µg/mL		8.13 - 13.06	-14.9 - 3.0	
FTC Plasma		FTC-110	5-ng/mL		8.05 - 20.18	-3.6 - 1.2	5, 25, 1000, 4000-ng/mL
FTC Urine		FTC-110	2.5-µg/mL		5.39 - 13.44	-6.1 - 4.0	----------
FTC Plasma		FTC-111	5-ng/mL		4.89 - 10.69	0.0 - 5.2	5, 25, 1000, 4000-ng/mL
FTC Plasma		FTC-112	10-ng/mL		2.41 - 3.54	-2.22 - -0.10	10, 25, 200, 2500-ng/mL
FTC Plasma		FTC-113	10-ng/mL		6.0 - 8.0	-2.8 - 2.1	10, 20, 50,

							500, 1000, 2000-ng/mL
FTC Plasma TDF Plasma		FTC-114	5-ng/mL 10ng/mL		4.09 - 13.86 5.17 - 14.43	-9.8 - 3.8 -9.0 - 2.4	5, 25, 1000, 4000-ng/mL 10, 24.9, 49.9, 99.7, 249.3, 498.5, 747.8, 997.0-ng/mL
FTC Plasma		FTC-303	10-ng/mL		6.24 - 11.23	-5.8 - 14.0	10, 100, 500, 1000, 2500-ng/mL

[a] Minimum quantitative level, ^ Methods developed by Glaxo Wellcome, assay documents not available

The sample analyses are acceptable.

5. Labeling Recommendations (suggested wording for selected sections)

CLINICAL PHARMACOLOGY

Pharmacodynamics:
The *in vivo* activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25 to 400 mg a day of EMTRIVA as monotherapy for 10 to 14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3 $\log_{10}$ at a dose of 25 mg QD and 1.7 $\log_{10}$ to 1.9 $\log_{10}$ at a dose of 200 mg QD or BID.

Pharmacokinetics:
The pharmacokinetics of emtricitabine were evaluated in healthy volunteers and HIV-infected individuals. Emtricitabine pharmacokinetics are similar between these populations.

Absorption: Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of EMTRIVA to 20 HIV-infected subjects, the (mean ± SD) steady-state plasma emtricitabine peak concentrations (C_{max}) were 1.8 ± 0.7 µg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 hr•µg/mL. The mean absolute bioavailability of EMTRIVA was 93%. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 µg/mL. The mean absolute bioavailability of EMTRIVA was 93%.

The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25 to 200-mg.

Effects of Food on Oral Absorption: EMTRIVA may be taken with or without food. Emtricitabine systemic exposure $AUC_{0-\infty}$) was unaffected when EMTRIVA was administered with food (an approximately 1000-kcal high-fat meal).

Distribution: *In vitro* binding of emtricitabine to human plasma proteins was <4% and independent of concentration over the range of 0.02 – 200 □g/mL. Approximately at peak plasma concentration, the mean plasma to blood drug concentration ratio was ~ 1.0 and the mean semen to plasma drug concentration ratio was ~ 4.0.

Metabolism: In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-emtricitabine, complete recovery of the dose was achieved in urine (~ 86%) and feces (~ 14%). Thirteen percent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~ 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~ 4% of dose). No other metabolites were identifiable.

Elimination: The plasma emtricitabine half-life is approximately 10 hours

The renal clearance of emtricitabine is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations:
The pharmacokinetics of emtricitabine were similar in male and female patients and no pharmacokinetic differences due to race have been identified.

The pharmacokinetics of EMTRIVA has not been fully evaluated in children or in the elderly.

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment, however, emtricitabine is not metabolized by liver enzymes, so the impact of liver impairment should be limited.

The pharmacokinetics of emtricitabine are altered in patients with renal impairment (See PRECAUTIONS). In patients with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, AUC of emtricitabine were increased due to a reduction in renal clearance (Table 1). It is recommended that the dosing interval for EMTRIVA be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see DOSAGE AND ADMINISTRATION).

Table 1. Mean ± SD Pharmacokinetic Parameters in Patients with Varying Degrees of Renal Function

Creatinine clearance (mL/min)	>80 (n=6)	50-80 (n=6)	30-49 (n=6)	<30 (n=5)	ESRD* <30 (n=5)
Baseline Creatinine clearance (mL/min)	107 ± 21	59.8 ± 6.5	40.9 ± 5.1	22.9 ± 5.3	8.8 ± 1.4
C_{max} (µg/mL)	2.2 ± 0.6	3.8 ± 0.9	3.2 ± 0.6	2.8 ± 0.7	2.8 ± 0.5
AUC (hr•µg/mL)	11.8 ± 2.9	19.9 ± 1.1	25.0 ± 5.7	34.0 ± 2.1	53.2 ± 9.9
CL/F (mL/min)	302 ± 94	168 ± 10	138 ± 28	99 ± 6	64 ± 12
CLr (mL/min)	213.3 ± 89.0	121.4 ± 39.0	68.6 ± 32.1	29.5 ± 11.4	-

*ESRD patients requiring dialysis
"-" = not applicable

Hemodialysis: Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Drug Interactions

At concentrations up to 14 fold higher than those observed in vivo, emtricitabine did not inhibit in vitro drug metabolism mediated by any of the following human CYP 450 isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation (uridine-5'-disphosphoglucuronyl transferase). Based on the results of these in-vitro experiments and the known elimination pathways of emtricitabine, the potential for CYP450 mediated interactions involving emtricitabine with other medicinal products is low.

EMTRIVA has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (DF), indinavir, stavudine, and famciclovir. Tables 2 and 3 summarize the pharmacokinetic effects of co-administered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of co-administered drug.

Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Co-administered Drug[1]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Stavudine	40 x 1	200 x 1	6	⇔	⇔	-
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-

5. All interaction studies conducted in healthy volunteers
6. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Emtricitabine[1]

Co-Administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Stavudine	40 x 1	200 x 1	6	⇔	⇔	-
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-

6. All interaction studies conducted in healthy volunteers
7. ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

INDICATION AND USAGE

EMTRIVA is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults.

PRECAUTIONS

Patients with Impaired Renal Function

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of EMTRIVA is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Drug Interactions

The potential for drug interactions with EMTRIVA has been studied in combination with indinavir, stavudine, famciclovir, and tenofovir disoproxil fumarate. There were no clinically significant drug interactions for either drugs in these studies (see CLINICAL PHARMACOLOGY, Drug Interactions).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to emtricitabine, an antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV infection. It is not known whether emtricitabine is secreted into human milk. Because of both the potential for HIV transmission and the potential for serous adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving emtricitabine.**

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Clinical studies of EMTRIVA did not contain sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

The dose of EMTRIVA for adults > 18 years of age is 200 mg once daily taken orally with or without food.

Dose Adjustment in Renal Impairment:

Significantly increased drug exposures were seen when EMTRIVA was administered to patients with renal impairment, ——— . Therefore the dosing interval of TRADENAME should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the following guidelines (see Table 8). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 8

Dosing Interval Adjustment in Patients with Renal Impairment

Hemodialysis: Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

HOW SUPPLIED

EMTRIVA is available as capsules. EMTRIVA capsules, 200 mg, are size 1 hard gelatin capsules with a blue cap and white body, printed with "200 mg" in black on the cap and "GILEAD" and the corporate logo in black on the body.

They are packaged in bottles of 30 capsules (NDC # xxxx-xxxx-xx) with induction sealed child-resistant closures.

Store at 25°C (77 F); excursions permitted to 15°C - 30°C (59°F-86°F) (see USP Controlled Room Temperature)

/S/ 02 July 2003

Jennifer L. DiGiacinto, Pharm.D.
Reviewer, Clinical Pharmacology
Division of Pharmaceutical Evaluation III, OCPB

Concurrence: /S/ 7-2-03

Kellie S. Reynolds, Pharm. D
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cc: HFD-530 /NDA 21-500
/MO/Fleischer
CSO/Yoerg
HFD-880 /JDiGiacinto
HFD-880 /TL/KReynolds

6. Appendices

6.1 Individual Study Reviews

6.1.1 Assay Validation & ADME Studies

Assay Validation Review

Background

Bioanalytical methods for the quantitation of FTC in human plasma and urine samples were developed and performed by Triangle Pharmaceuticals, Inc. (Triangle) for analysis of all clinical samples, except for one study (Study 143-001) conducted by — — in 1994. The assay used by — for the determination of FTC in plasma and urine samples was by an —

The assay methods used for determination of FTC concentrations by Triangle were — followed by — analysis for plasma samples and — — followed by — analysis for urine samples or dilution of the urine followed by direct injection onto — The methods at times were modified slightly to accommodate the specific needs of individual studies; however, assay cross validation was performed prior to implementation to ensure the modified assay method generated equivalent results as the original method.

Determination of FTC in Human Plasma

Three different methods were used to determine FTC levels in human plasma. One was used for the analysis of FTC alone, another for the simultaneous analysis of FTC and emivirine, and another for the simultaneous analysis of FTC, zidovudine (ZDV), and stavudine (d4T).

Determination of FTC (Alone) in Human Plasma

Bioanalytical method no. 6447 (versions 1, 2, and 3) was the principal method employed when FTC was the only analyte to be measured. This is a validated — — bioanalytical method conducted by Triangle. This method was used for the analysis of FTC plasma samples from Studies FTC-101, FTC-105, FTC-106, FTC-107, FTC-108, FTC-109, FTC-110, and FTC-111.

Human plasma was diluted with internal standard (lamivudine [3TC] 750-ng/mL) and thoroughly mixed.

Validation of Bioanalytical Method No. 6447 (Version 1, 2, and 3)

Parameter	Observation	Comment
Linear range	— ng/mL	Satisfactory
*(r)	for all calibration curves	Satisfactory
LLOQ	—ng/mL	Satisfactory
Specificity		Satisfactory
Stability (freeze-thaw)	Stable for 154 days when stored at - 80° C	Satisfactory

- Linear Correlation Coefficient

Analyte	Precision*		Accuracy**	
	Intra-assay	Inter-assay	Intra-Assay	Inter-Assay
FTC	2.09% to 12.12%	4.89% to 10.69%	-2.0% to 6.4%	0.0% to 5.2%

*Precision is expressed as %CV
**Accuracy is expressed as % bias

The assay is acceptable.

Determination of FTC and Emivirine (MKC-442) in Human Plasma and Semen
Bioanalytical method no. 5480 (version 1) was used to assay for FTC and MKC-442 levels in human plasma samples in Studies FTC-104. This assay is applicable to measure FTC only in studies FTC-102, and FTC-303 pharmacokinetic (PK) sub-study. Additionally, this method was used for the assay of FTC levels in human semen samples from Study FTC-106.

This is a validated [redacted] followed by [redacted] by [redacted]

Validation of Bioanalytical Method No. 5480 (Version 1)

Parameter	Observation	Comment
Linear range	[redacted] ng/mL	Satisfactory
*(r)	[redacted] for all calibration curves	Satisfactory
LLOQ	[redacted] ng/mL	Satisfactory
Specificity	/	Satisfactory
Stability (freeze-thaw)	Stable for 154 days when stored at - 80° C	Satisfactory

* Linear Correlation Coefficient

Analyte	Precision*		Accuracy**	
	Intra-assay	Inter-assay	Intra-Assay	Inter-Assay
FTC	4.08% to 7.11%	3.74% to 9.19%	-1.3% to 8.1%	-0.4% to 1.8%

*Precision is expressed as %CV
**Accuracy is expressed as % bias

The assay is acceptable.

Reviewer Comment: With regards to the validation of the semen assay, human plasma was used as a surrogate matrix for the analysis of the semen samples because semen is a difficult to obtain matrix. Therefore, there is no data from the validation of this assay.

Determination of FTC, ZDV, and d4T in Human Plasma

Bioanalytical method no. 7968 (version 1) was used to assay for FTC, ZDV, and d4T levels in human plasma samples from Study FTC-103. The compounds of interest are separated from the plasma using — resolved by — — and detected by — This method was developed and validated by Triangle.

Validation of Bioanalytical Method No. 7968 (Version 1)

Parameter	Observation	Comment
Linear range FTC/ZDV/d4T	— ng/mL/ — ng/mL/ ng/mL	Satisfactory
*(r)	for all calibration curves	Satisfactory
LLOQ FTC/ZDV/d4T	— ng/mL/ — ng/mL/ — ng/mL	Satisfactory
Specificity	/	Satisfactory
Stability (freeze-thaw)	Stable for 154 days when stored at - 80° C	Satisfactory

* Linear Correlation Coefficient

Analyte	Precision*		Accuracy**	
	Intra-assay	Inter-assay	Intra-Assay	Inter-Assay
FTC	4.00% to 7.19%	4.26% to 6.46%	-0.4% to 7.9%	-1.2% to 4.8%
ZDV	+NA to 4.51%	6.17% to 9.15%	-5.1% to 1.4%	-1.6% to 3.6%
d4T	5.47% to 13.58%	7.50% to 11.85%	-8.4% to 3.4%	-6.6% to 2.9%

*Precision is expressed as %CV

**Accuracy is expressed as % bias

+ Two of four of the LLOQ pool passed the acceptance criteria, therefore, %CV is not applicable to this sample set.

- The assay is acceptable.

Determination of FTC in Human Urine

Bioanalytical method no. M-00-TP0006-01 was used to analyze urine samples from Studies FTC-105, FTC-106, FTC-107, FTC-108, and FTC-110. This is a — technique using an — as the detector. Due to high levels of FTC in the human urine samples, the sample preparation technique was changed from a — to a simple dilution and injection procedure using water as the diluent. This assay is an improved assay compared to the original assay used to measure FTC in urine in the earlier clinical Study FTC-101.

Validation of Bioanalytical Method No. M-00-TP0006-01

Parameter	Observation	Comment
Linear range FTC	— µg/mL	Satisfactory
*(r)	for all calibration curves	Satisfactory
LLOQ FTC	— µg/mL	Satisfactory
Specificity	/	Satisfactory
Stability (freeze-thaw)	Stable for 294 days when stored at - 80° C	Satisfactory

* Linear Correlation Coefficient

Determination of FTC in Human Urine Continued

Analyte	Precision*		Accuracy**	
	Intra-assay	Inter-assay	Intra-Assay	Inter-Assay
FTC	1.84% to 5.56%	5.22% to 9.67%	-9.1% to 8.0%	-4.0% to 3.3%

*Precision is expressed as %CV
**Accuracy is expressed as % bias

The assay is acceptable.

Comment to Applicant
None.

Dissolution Study

Proposed Dissolution Method and Specification
The proposed dissolution method for EMTRIVA™ 200-mg capsule is as follows:

Apparatus USP 2 (paddle)
Rotation Speed 50 rpm
Temperature: 37.5° C ± 0.5° C
Medium Tier 1: 900 mL of 0.1 N HCl
Medium Tier 2: 900 mL of 0.1 N HCl containing ≤ 750,000 USP units/L pepsin
Sampling Time: 30 minutes
Sample Amount: One capsule per vessel
Filter:
Sample Volume: 10 mL
Analytical Method:

The proposed dissolution specification for EMTRIVA™ 200-mg capsules is
Q = % dissolved in 30 minutes.

Background
Emtricitabine (FTC) has a pKa of 2.65 ± 0.01 and the octanol/water partition coefficient of FTC expressed as the Log P value is -0.43. The solubility of FTC is > 60 mg/mL throughout the pH range (See Table 1 below). To maintain sink conditions a solubility value of 0.67 mg/mL is required for this drug product.

Table 1. Solubility of FTC at 25° C in Various Solvents and in Aqueous Solution

Solvent/Solution	Solubility (mg/mL)
Water	112
Methanol	113
Acetonitrile	4
0.1 N HCl	170
0.1 N NaOH	115
Isopropyl Acetate	0.3
Phosphate Buffer, pH 4.0	61.6
Phosphate Buffer, pH 6.0	61.3
Phosphate Buffer, pH 7.0	61.2

Materials and Reagents

EMTRIVA™ Capsule, 200-mg **(Formulation B)**

Abbott Laboratories™ Lot #	Corresponding Triangle Lot #
Lot 66-382-AR	TP-0006-99125
Lot 70-035-4Q	TP-0006-00205
Lot 71-040-4Q	TP-0006-00207
Lot 75-042-4Q	TP-0006-01031
Lot 75-043-4Q	TP-0006-01047
Lot 75-044-4Q	TP-0006-01048
Lot 78-045-4Q	TP-0006-01109

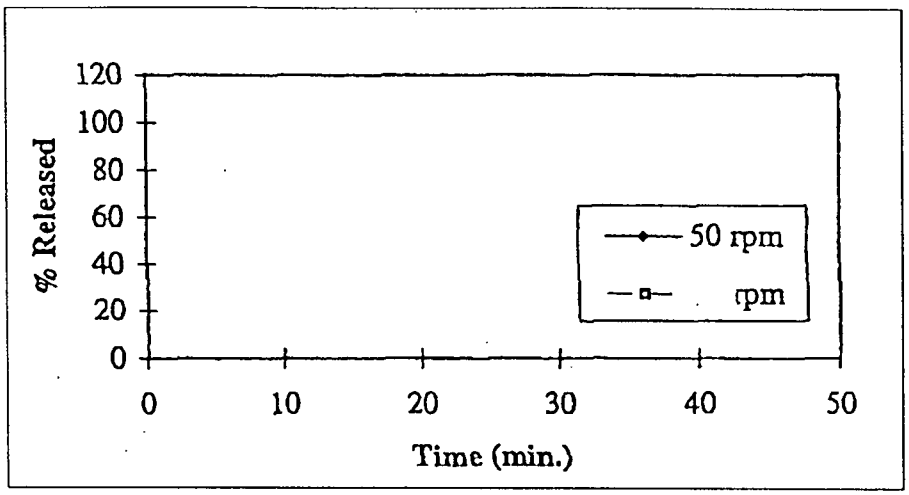
EMTRIVA™ Capsule, 100-mg **(Formulation C)**
TP-0006-00120

Dissolution Test Method Justification

USP Apparatus 2 (paddle) was chosen by the Sponsor for convenience purposes. The simplicity, robustness, and global acceptance were reasons given for their selection. Due to the tendency for capsule dosage forms to float, a —— —— is used to keep the capsule in the bottom of the dissolution vessel.

The dissolution performance of the pivotal bioequivalence (BE) Lot (TP-0006-00205) using rotational speeds of 50 rpm and —— were compared. The increased paddle speed had no impact on the release; therefore, a rotation speed of 50 rpm was chosen. (See Figure 1 below).

Figure 1. Effect of Apparatus Agitation on the Dissolution Performance of EMTRIVA™ Capsules, 200-mg (TP-0006-00205 BE Lot) in 0.1 N HCl (N= 12)



The selection of the appropriate dissolution medium for EMTRIVA™ Capsules, 200-mg was based on the desire to test at sink conditions, utilize a pH of physiological relevance, and the potential need for a medium that would accommodate proteolytic enzymes.

Since emtricitabine is highly soluble, it is expected to dissolve rapidly in the upper gastrointestinal track (GI). Therefore, a dissolution medium mimicking the pH of the stomach is physiologically relevant.

Earlier in the IND phase, the Applicant discussed with the Agency the potential for gelatin cross-linking to occur with the capsules when exposed to heat, humidity, and some oxidative agents. To date there has been no evidence of gelatin cross-linking (pellicle) with this formulation; however, pellicle formation was observed with a previous formulation. The Applicant has developed a tier 2 dissolution method (reference is made to correspondence with the FDA dated 17April2000, IND [SN156] and corresponding FDA fax dated 11May2000). As specified in USP 24 <711>, Tier 2 dissolution methods incorporate the use of proteolytic enzymes (pepsin). It is desirable to maintain the medium at a pH that is optimal for the chosen enzyme. An acidic medium (pH 1-3) provides the best environment for pepsin.

A dissolution medium of 0.1 N HCl is proposed for the tier 1 dissolution test.

Dissolution Performance in Standard Dissolution Media

Figure 2. Dissolution Profiles for EMTRIVA™ Capsules, 200-mg Lot #TP-0006-00205 (Pivotal BE Lot, n=12)

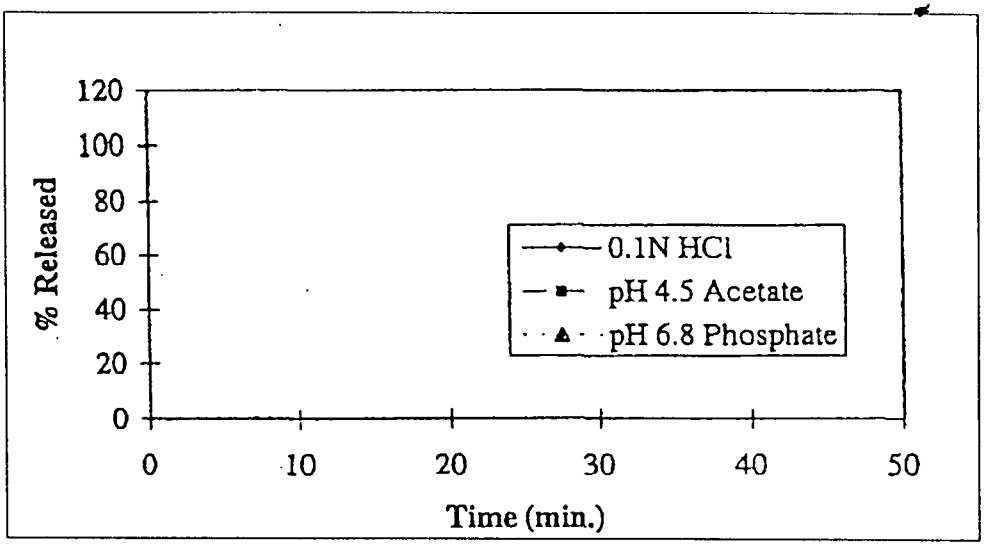


Table 2. Dissolution Profile Data for EMTRIVA Capsules, 200-mg, Lot # TP-0006-00205 (Pivotal BE Lot FTC-111), Medium: 0.1 N HCl

	Percent Label Claim Dissolved			
Run	10	20	30	45
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	66.7	100.5	101.7	101.7
S.D.	4.5	2.4	2.3	2.4
C.V.	6.7	2.4	2.3	2.3

Table 3. Dissolution Profile Data for COVIRACIL™ Capsules, 200-mg, Lot TP-0006-00205 (Pivotal BE Lot), Medium: pH 4.5 Acetate Buffer

	Percent Label Claim Dissolved			
Run	10	20	30	45 min.
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	89.5	100.2	100.8	100.8
S.D.	3.8	2.1	2.1	2.1
C.V.	4.3	2.1	2.0	2.1

Table 4. Dissolution Profile Data for EMTRIVA™ Capsules, 200-mg, Lot # TP-0006-00205 (Pivotal BE Lot), Medium: pH 6.8 Phosphate Buffer

	Percent Label Claim Dissolved			
Run	10	20	30	45 min.
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	53.1	95.7	100.7	101.1
S.D.	5.4	2.9	2.6	2.8
C.V.	10.1	3.0	2.6	2.8

Reviewer Comment: *The Applicant's dissolution medium selection of 0.1 N HCl is acceptable.*

Dissolution Performance of Registration Lots

Tables 1 through 3 contain individual run data for the three registration lots of EMTRIVA™ Capsules, 200-mg.

Table 5. Dissolution Profile Data for EMTRIVA™ Capsules, 200-mg Batch# TP-0006-00133, Medium 0.1 N HCl

	Percent Label Claim Dissolved			
Run	10	20	30	45 min.
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	102.4	103.0	103.1	103.3
S.D.	1.4	1.3	1.2	1.3
C.V.	1.3	1.2	1.2	1.2

Table 6. Dissolution Profile Data for EMTRIVA Capsules, 200-mg, Lot # TP-0006-00205 (Pivotal BE Lot FTC-111), Medium 0.1 N HCl

	Percent Label Claim Dissolved			
Run	10	20	30	45
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	66.7	100.5	101.7	101.7
S.D.	4.5	2.4	2.3	2.4
C.V.	6.7	2.4	2.3	2.3

Dissolution Performance of Registration Lots Continued

Table 7. Dissolution Profile Data for EMTRIVA Capsules, 200-mg, Lot # TP-0006-00207, Medium 0.1 N HCl

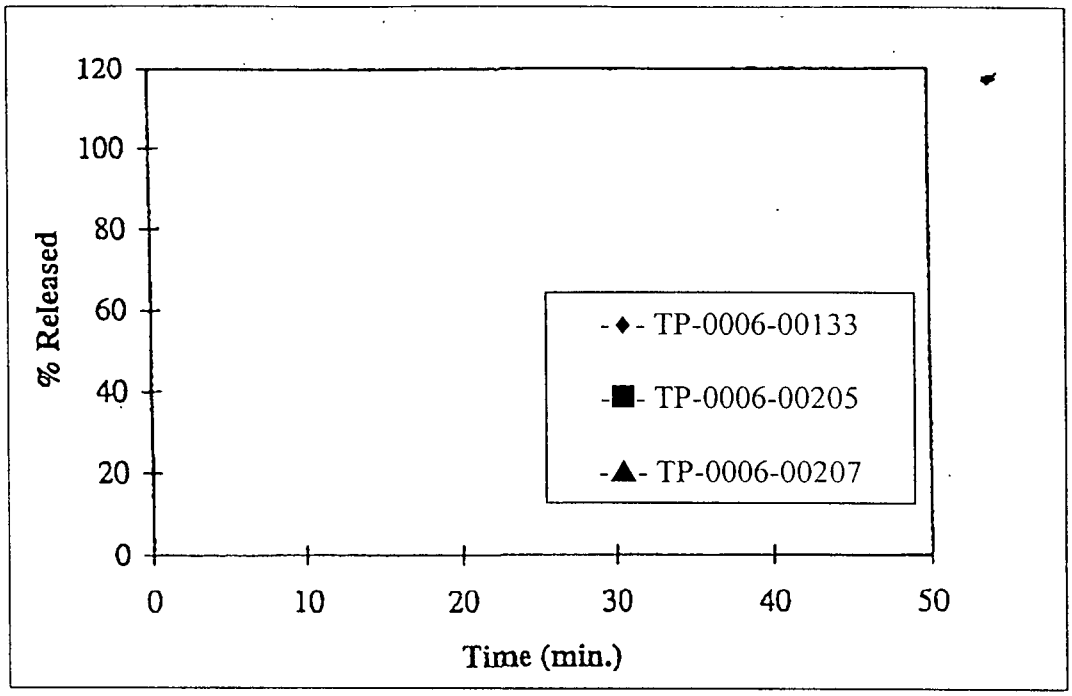
	Percent Label Claim Dissolved			
Run	10	20	30	45 min.
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	31.9	77.2	94.7	100.4
S.D.	5.4	5.6	6.1	3.1
C.V.	16.8	7.3	6.5	3.1

Table 8. Dissolution Profile Comparisons Data, Mean (SD), for EMTRIVA™ Capsules, 200-mg, Registration Lots

	% Label Claim Dissolved			
Lot	10 Minutes	20 Minutes	30 Minutes	40 Minutes
TP-0006-00133	102.4 (1.4)	103.0 (1.3)	103.1 (1.2)	103.3 (1.3)
TP-0006-00205	66.7 (4.5)	100.5 (2.4)	101.7 (2.3)	101.7 (2.4)
TP-0006-00207	31.9 (5.4)	77.2 (5.6)	94.7 (6.1)	100.4 (3.1)

Complete release for Lot #'s TP-0006-00133 and TP-0006-00205 was achieved in 30 minutes; complete release for Lot # TP-0006-00207 was achieved in 45 mintues.

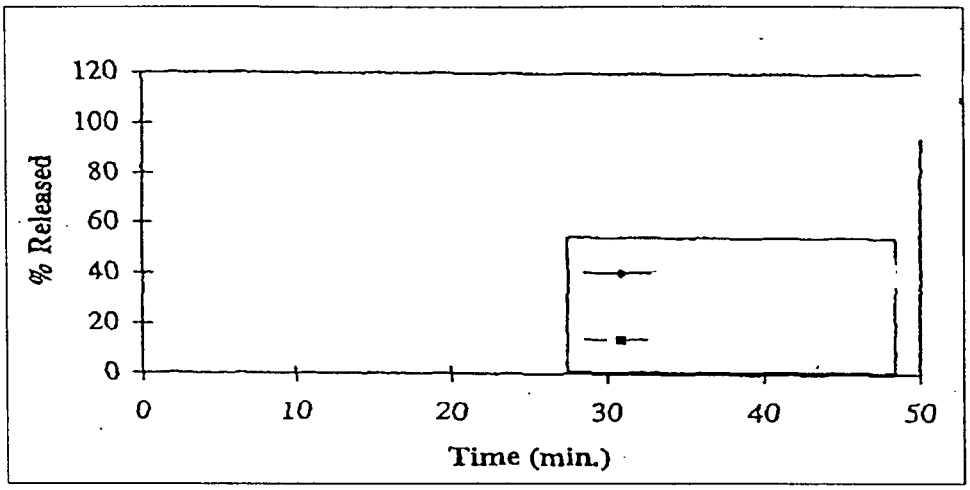
Figure 3. Dissolution Profiles of EMTRIVA™ Capsules, 200-mg, Registration Lots (n=12)



The — Lot # TP-0006-00133 were — using a — whereas the — from the second and third registration lots, TP-0006-00205 and TP-0006-00207 were . The difference in dissolution rate is attributed to — size. Experimentally, the Applicant — Lot # TP-0006-00207, using — to decrease the — particle size. Figure 3 graphically presents the impact on the dissolution profile.

APPEARS THIS WAY
ON ORIGINAL

Figure 4. Effect on ——— on Dissolution Performance of ———
Lot # TP-0006-00207



Dissolution Performance of Registration Lots Continued

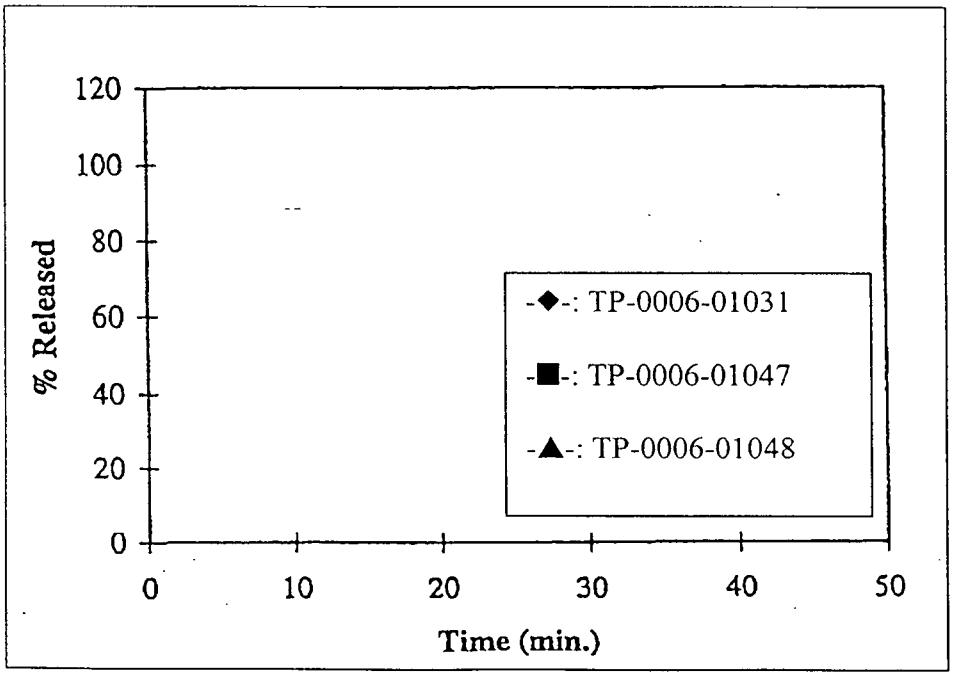
The reduction in ——— size has resulted in a dissolution profile similar to Lot #'s TP-0006-00133 and TP-0006-00205. The proposed commercial process specifies ———

Dissolution Performance of Post-Registration Lots

The dissolution profiles for 4 commercial scale lots manufactured after the last registration Lot 0006-00207 is shown in Figure 4.

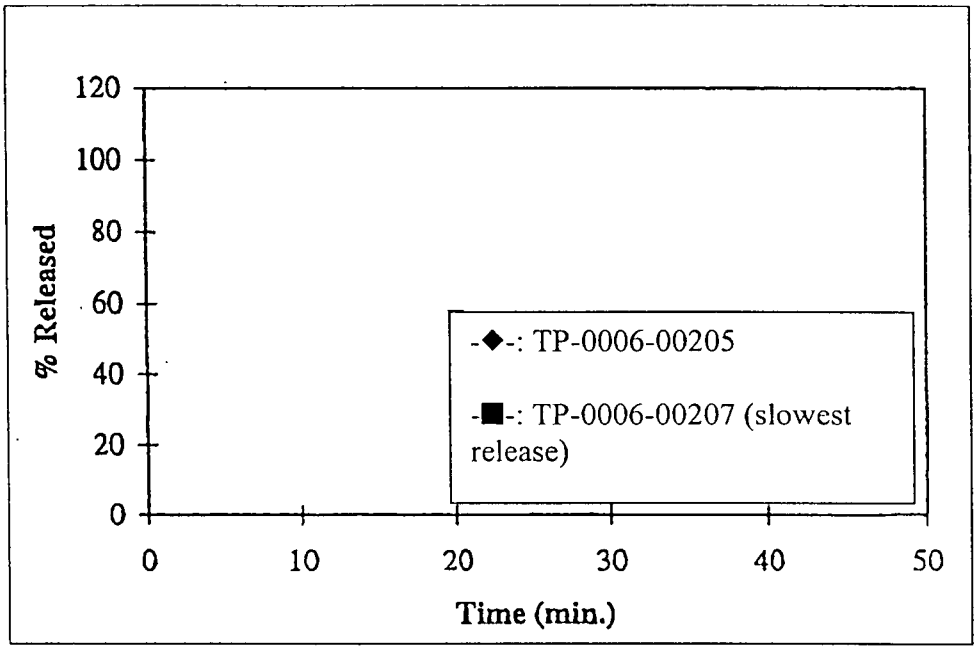
Figure 5. Dissolution Profiles for EMTRIVA™ Lots Manufactured Post Registration (n=12 for Lot 78-045-4Q, n=6 for all others)

Dissolution Performance of Pivotal BE Lot and Reference Products



EMTRIVA™ Lot # TP-0006-00205 was evaluated in the pivotal BE study, FTC-111, using Lot # TP-0006-00120 (100-mg capsule Formulation C) as the reference product. The dissolution profiles for these two lots are plotted with the slowest releasing registration Lot, TP-0006-00207 in Figure 5.

Figure 6. Dissolution Profiles for EMTRIVA™ Capsules, 200-mg, Lot # TP-0006-00205, TP-0006-00207, and TP-0006-00120 (100-mg capsules) n=12



Specification Justification

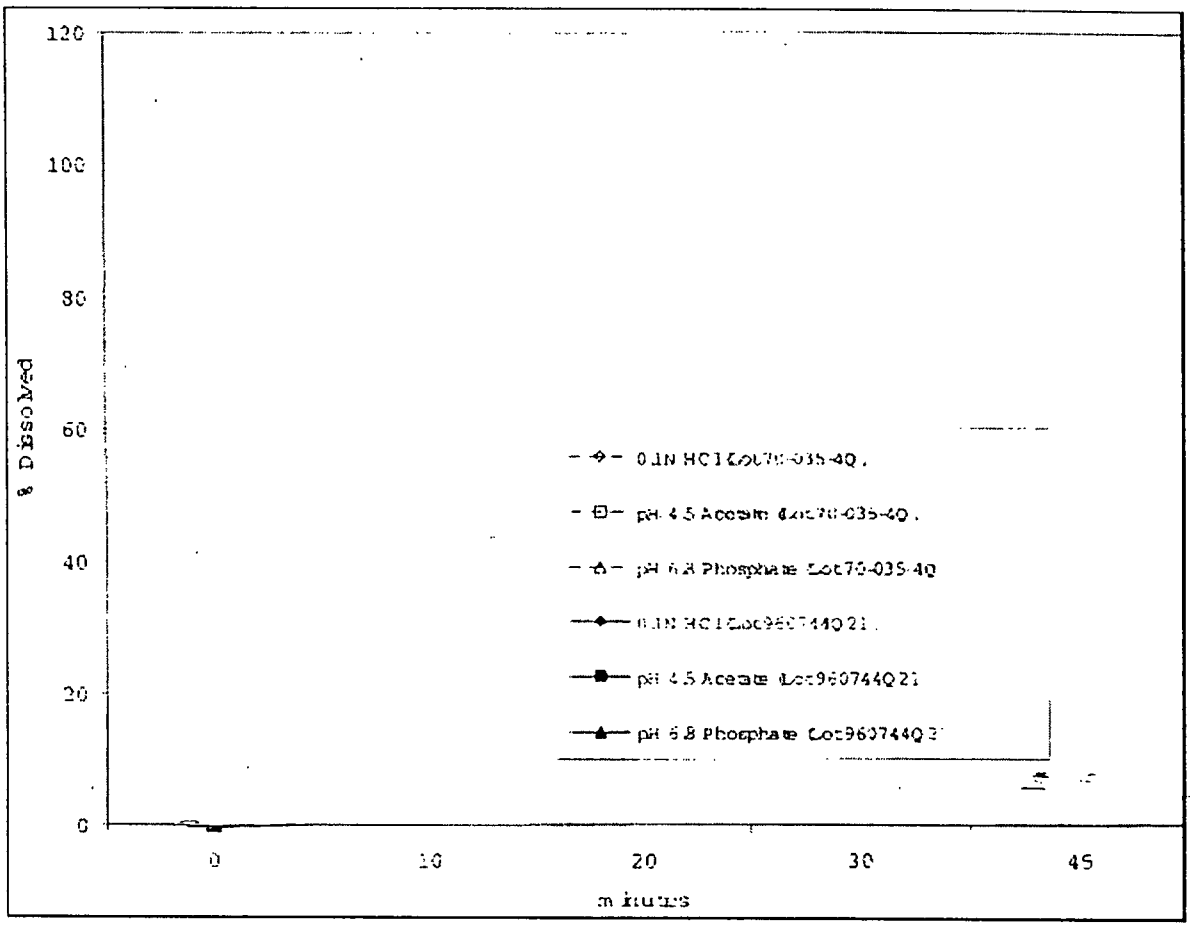
The Applicant proposes a specification of Q= % in 30 minutes for dissolution testing of EMTRIVA™ Capsules, 200-mg. The pivotal BE Lot achieves complete dissolution in 30 minutes. This specification is based on *in vitro* dissolution data for registration lots TP-0006-99125, TP-0006-00205, and TP-0006-00207 and *in vivo* performance lots with differing dissolution profiles. Specifically, registration Lot # TP-0006-00207, which meets the proposed specification, exhibited a dissolution profile similar to the reference Lot from FTC-111 (pivotal BE study) Lot # TP-0006-00120. TP-0006-00205 was BE to TP-0006-00120 in the FTC-111 pivotal BE study.

Reviewer Comment: The Applicant defends their proposed specification of Q= % L;dissolved in 30-minutes by the similarities of the dissolution profiles for the reference product studied in the pivotal BE study FTC-111 to the slowest releasing Lot TP-0006-00207 along with the in vivo performance of the differing lots. Subsequently, the Applicant has which decreases the particle size of emtricitabine and changes the % dissolved in minutes. The Applicant did not provide dissolution data using all 3 media with the intended to be marketed EMTRIVA™ These additional dissolution data were requested from the Applicant.

Applicant's Response to Our Request

Figure 6 below includes the requested dissolution profiles for the intended to-be-marketed FTC capsule formulation tested in three different dissolution media. The capsule batch (Lot # 960744Q21) presented was manufactured using the intended commercial manufacturing process ——— For comparison, Figure 6 also displays the dissolution profiles of the capsule batch (Lot # TP-0006-00205) used in the pivotal BE study FTC-111.

Figure 7. Dissolution Profiles of FTC Capsules, 200-mg, Commercial Formulation Process Lot # 960744Q21, ——— and Bioequivalence Batch Lot TP-0006-00205 in Dissolution Media of 0.1 N HCl, pH Acetate Buffer, and pH 6.8 Phosphate Buffer



The results show FTC capsules manufactured with the ——— exhibit good dissolution across the physiological pH range and exhibit a dissolution profile consistent with that of the batch used in the pivotal BE study.

The individual dissolution data supporting the dissolution profile of the intended to-be marketed formulation ——— as determined in dissolution media of 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer are provided in Tables 5-7.

Table 9. Dissolution Profile Data for FTC Capsules, 200-mg, Lot 960444Q21, Commercial Process _ . . in 0.1 N HCl Dissolution Medium

	Percent Label Claim Dissolved			
Run	10	20	30	45 min
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean			102	103
SD			1.0	0.9
%RSD			1.0	0.9

Table 10. Dissolution Profile Data for FTC Capsules, 200-mg, Lot 960444Q21, Commercial Process in pH 4.5 Acetate Buffer Dissolution Medium

	Percent Label Claim Dissolved			
Run	10	20	30	45 min
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	81	102	102	102
SD	0.6	0.9	0.8	0.8
%RSD	0.7	0.9	0.8	0.8

Table 11. Dissolution Profile Data for FTC Capsules, 200-mg, Lot 960444Q21, Commercial Process in pH 6.8 Phosphate Buffer Dissolution Medium

	Percent Labe Claim Dissolved			
Run	10	20	30	45 min
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	42	85	100	103
SD	6.8	8.6	3.3	1.1
%RSD	16.3	10.1	3.3	1.1

Reviewer Comment: The applicant has provided the requested dissolution data for the intended to-be marketed formulation of FTC.

Conclusion: The dissolution method for EMTRIVA™ is as follows:

Apparatus	*USP 2 (paddle)*
Rotation Speed	*50 rpm*
Temperature:	*37.5° C ± 0.5° C*
Medium Tier 1:	*900 mL of 0.1 N HCl*
Medium Tier 2:	*900 mL of 0.1 N HCl containing ≤ 750 000 USP units/L pepsin*
Sampling Time:	*30 minutes*
Sample Amount:	*One capsule per vessel*
Filter:	
Sample Volume:	*10 mL*
Analytical Method:	

The dissolution specification for EMTRIVA™ 200-mg capsules is Q = ( )% dissolved in 30 minutes.

Mass Balance Study (FTC-106)

Objectives

Primary-

- To determine the mass-balance or recovery of an orally administered dose of emtricitabine (FTC) by measuring ^{14}C-labeled materials in urine and fecal samples derived from ^{14}C-labeled FTC given under a steady state condition
- To estimate the extent of oral absorption of FTC following a single dose of ^{14}C-labeled FTC given under a steady state condition
- To evaluate the extent of FTC distribution in semen
- To determine the metabolic profiles of FTC in man
- To determine the urinary and fecal excretion profiles of FTC and its metabolites

Secondary-

- To explore the pharmacokinetics (PK) of FTC-5'-triphosphate (TP), the active moiety of FTC, in peripheral blood mononuclear cells (PBMCs) after a single dose of ^{14}C-labeled FTC given under a steady state condition

Study Design

This was an open-label, mass-balance study conducted at a single center in the USA to evaluate the absorption, distribution, metabolism, and excretion (ADME) of ^{14}C-labeled FTC following a single oral dose of ^{14}C-labeled FTC under a steady state condition in 6 healthy male volunteers. FTC doses administered on PK days (Day 1 and Day 11) were given under fasted conditions.

Day 1

Volunteers received a single 200-mg FTC dose (2 x 100-mg FTC capsule) and then followed with a 48-hour post dose serial PK sample collection of blood and urine.

Days 3-10

Volunteers received a daily 200-mg FTC dose (2 x 100-mg capsule) each morning on days 3 through 10 in order to reach steady state conditions prior to the administration of ^{14}C-labeled FTC.

Day 11

Volunteers received a single oral doe of ^{14}C-labeled FTC (250 μCi in a sweetened, strawberry-flavored oral solution formulation containing 200-mg unlabeled FTC). Following the ^{14}C-labeled FTC administration, volunteers began a 7-day serial sample collection period, during which serial samples of blood/plasma, blood/PBMCs, cumulative urine and stools were collected at pre-determined intervals.

PK Sample Collection

Day 1: Blood samples were collected at pre-dose and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, and 48 hours post-dose.

Cumulative urine samples were collected at pre-dose and over the intervals of 0-6, 6-12, 12-24, 24-36, and 36-48 hours post-dose.

Days 5, 7, and 9: A single blood sample was collected prior to the morning dose to measure trough values.

Day 11: Blood samples were collected at pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours on Day 11 and every 12 hours post-dose there after up until 168 hours post-dose (7-days).

PBMCs were collected at pre-dose and at 1, 3, 6, 9, 12, and 24 hours on Day 11 and then every 24 hours post-dose there after until 96 hours (4-days).

Cumulative urine samples were collected at pre-dose and over the intervals of 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours post dose, and then every 24 hours thereafter.

Cumulative stool samples were collected at pre-dose and over daily (24-hour) intervals post-dose.

One semen sample taken on Day 11 at approximately 1.5 hours post-dose (to coincide with C_{max}).

Test Product, Strength of Drug Product, and Batch Numbers

- 100-mg COVIRACIL™ capsules (Lot No. TP-0006-99044)
- 10-mg/mL COVIRACIL™ oral solution (Lot No. TP-000/96/WW)
- ^{14}C-labeled FTC with a specific activity of 51mCi/mmol (0.206 mCi/mg) [Lot No. TP-0006-99084 (Manufacture's Lot No. 3361001)]

Mass Balance Study FTC-106 Results

FTC PK and Urinary Excretion on Days 1 and 11 as Determined by [redacted]

The key mean PK parameter estimates for plasma FTC after a single 200-mg oral dose on Day 1 and at steady state (Day 11) following 200-mg daily doses of FTC are summarized below in Table 1.

Table 1. Mean PK Parameter Estimates for Plasma FTC Determined by [redacted]

Study Day	Statistic	C_{max} (µg/mL)	t_{max} (hr)	AUC_{0-t} (µg·hr/mL)	$AUC_{0-\infty}$ (µg·hr/ml)	$t_{1/2}$ (hr)	CL/F (mL/min)
Day 1 200-mg N=6	Mean	2.14	1.17	10.11	10.42	12.0	322
	%CV	15	22	6	6	23	6
Study Day	**Statistic**	**$C_{ss,max}$ (µg/mL)**	**$t_{ss,max}$ (hr)**	**$C_{ss,min}$ (µg/mL)**	**AUC_{τ} (µg·hr/ml)**	**$t_{1/2}$ (hr)**	**CL_{ss}/F (mL/min)**
Day 11 200-mg QD N=5	Mean	1.72	1.00	0.073	10.04	10.2	339
	%CV	16	0	28	18	19	20

- FTC disposition follows linear kinetics and steady-state was achieved after 4 consecutive daily doses
- The steady state plasma trough concentrations were 5-fold higher than the mean *in vitro* IC_{90} value (0.014 µg/mL)

Reviewer Comment: The lower C_{max} and AUC achieved on Day 11 compared to Day 1 may be due to the volunteers receiving the FTC oral solution formulation on Day 11 versus the FTC capsules on Day 1. Study FTC-110 demonstrated the oral solution has a lower bioavailability (BA) compared to the FTC capsule (approximately 24% less).

Table 2 below summarizes the mean urinary excretion data of FTC (by [redacted] on Days 1 and 11.

Table 2. Mean Urinary Excretion Values for FTC

Study Day	Statistic	Cumulative % of Dose Excreted as FTC (0-last sample)	Cumulative % of Dose Excreted as FTC (0-24 hr)	CL_R (mL/min)	Ratio of CL_R:CL/F
Day 1 Single Dose N=6	Mean	58.7	57.4	194	0.61
	%CV	16	18	18	16
Day 11 Steady State N=5	Mean	75.9	62.1	207	0.62
	%CV	15	14	14	14

- Greater than 60% of an oral dose of FTC was excreted as unchanged FTC in urine
- The majority of the dose was excreted within 24 hours following a single dose or at steady state
- Average CL_R value of FTC was consistently greater than estimated creatinine clearance (CL_{cr}), indicating renal tubular secretion of FTC

Pharmacokinetics and Excretion of ^{14}C-Radioactivity on Day 11 as Determined by Liquid Scintillation Counting (LSC) and ^{14}C-FTC as determined by — Radiochemical Assay (RCA)

Table 3 below summarizes the key mean PK estimates for plasma total ^{14}C-Radioactivity after a single oral dose (200-mg) of FTC containing 250 μCi of ^{14}C-FTC and PK estimates for ^{14}C-FTC after a single oral dose of FTC (200-mg administered as an oral solution).

Table 3. Mean Pharmacokinetic Parameters of ^{14}C-Radioactivity (Day 11) Determined by LSC and ^{14}C-FTC (Day 11) Determined by — RCA

Day 11 Dose	Statistic	C_{max} (μg/mL)	t_{max} (hr)	AUC_{0-t} (μg·hr/mL)	$AUC_{0-\infty}$ (μg·hr/ml)	t½ (hr)	CL/F (mL/min)
^{14}C-radioactivity 250 μCi N=5	Mean	1.87	1.20	12.87	14.04	28.1	242
	%CV	13	23	21	18	17	19
^{14}C-FTC 200-mg N=5	Mean	1.53	1.20	6.30	7.68	2.80	445
	%CV	16	48	19	19	16	21

- The mean plasma/blood ratio for ^{14}C-radioactivity ranged from 0.96-1.11
- — RCA is not as sensitive (LLOQ = — μg equiv/mL) as the — method (0.005 μg/mL) and this could explain why the ^{14}C-FTC concentrations were much less than those determined for FTC by —
- The PK parameter estimates for the total ^{14}C-radioactivity in plasma were similar to those determined for plasma FTC by — except for the AUC_{0-inf} value for total ^{14}C-radioactivity was greater than the AUC_{τ} value for FTC. The Applicant suggests these differences may be due to experimental errors between different assays and standards used or it could be due to the presence of metabolites in plasma that may have a longer t½ than the parent drug.
- The t½ value for plasma ^{14}C-radioactivity was estimated up to 60 hours post-dose and was greater than the t½ determined for FTC over a clinically relevant time (24 hours), but was similar to the FTC t½ on Day 11 when estimated up to the final time point (108 hours) post-dose

Figure 1 below depicts the mean plasma concentration vs. time curve for total ^{14}C-radioactivity, ^{14}C-FTC, and ^{14}C-metabolites (M1, M2, and M3) of FTC following a single oral dose of ^{14}C-FTC on Day 11.

Figure 1. Mean Plasma Concentration vs. Time Curves for Total ^{14}C-Radioactivity, ^{14}C-FTC, and ^{14}C-Metabolites (M1, M2, and M3) of FTC Following a Single Oral Dose of ^{14}C-FTC on Day 11

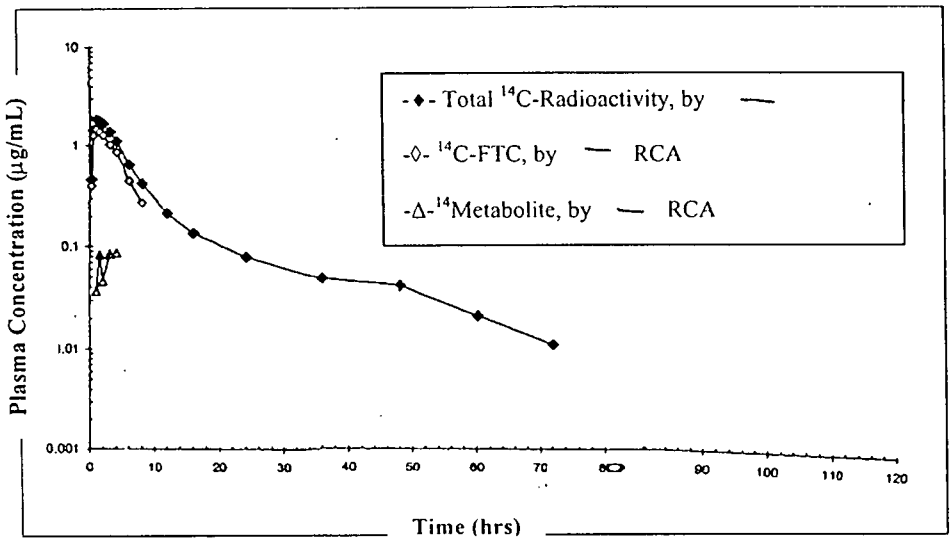


Table 4 below summarizes the mean urinary and fecal recovery and urinary excretion data of total ^{14}C-radioactivity (by LSC) on Day 11.

Table 4. Mean Urinary and Fecal Recovery and Urinary Excretion Data of Total ^{14}C-Radioactivity (by LSC) on Day 11

Sample Matrix	Statistic	Total Cumulative % of Radioactive Dose Excreted	Cumulative % of Radioactive Dose Excreted (0-24 hr)	Average Cl_R of ^{14}C-radioactivity (mL/min)	Ratio of CL_R: CL/F
Urine (N=5)	Mean	85.8	72.4	206	0.86
	%CV	8	11	15	8
Feces (N=5)	Mean	13.7	0.0	-	-
	%CV	29	-	-	-
Urine and Feces	Mean	99.6	72.4	-	-
	%CV	3	11	-	-

- The overall recovery of ^{14}C-radioactivity dose was almost complete, > 99% dose recovered in urine and feces
- The majority of the radioactive dose recovered in urine was excreted within 24 hours post dosing on Day 11 (> 84%) and an additional 10% was excreted in urine from 24-72 hours post-dose
- The ^{14}C-radioactive dose was slowly excreted in feces with no dose recovered in the first 24 hours post-dose and with the majority of the radioactive dose recovered in feces during the 48-72 hour and 72-96 hour post-dose fecal sample collections (53% and 33%, respectively, of the total fecal recovery)

Urinary and Fecal Recovery and Urinary Excretion Data of ^{14}C-FTC and ^{14}C-Metabolites by — RCA on Day 11

Table 5 below summarizes the mean urinary and fecal recovery and the urinary excretion data of ^{14}C-FTC and ^{14}C-Metabolites on Day 11 using the — RCA assay.

Table 5. Mean Urinary and Fecal Recovery Data and Urinary Excretion Data of ^{14}C-FTC and ^{14}C-Metabolites by — RCA on Day 11

Sample Matrix	Statistic	*Total Cum. % of ^{14}C Dose Recovered	Cum. % of ^{14}C Dose Excreted as ^{14}C-FTC	Cum. % of ^{14}C Dose Excreted as ^{14}C-M1	Cum. % of ^{14}C Dose Excreted as ^{14}C-M2	Cum. % of ^{14}C Dose Excreted as ^{14}C-M2	Cum. % of ^{14}C Dose Excreted as ^{14}C-M1, M2, & M3
Urine N =5	Mean	85.8	65.4	0.28	8.67	3.99	12.9
	%CV	8	6	22	36	24	26
Feces N = 5	Mean	13.7	13.2	0.003	0.008	0.002	0.013
	%CV	29	31	224	145	224	Not calc.
Urine & Feces	Mean	99.6	78.6	0.28	8.68	3.99	12.9
	%CV	3	3	Not calc.	Not. calc.	Not calc.	Not calc.

*LSC method was used to calculate these values
Not calc. = not calculated

- The difference (approximately 7.5% of the dose) between the % of total ^{14}C-radioactivity dose recovered in urine (85.5%) and the % of dose recovered as ^{14}C-FTC and it's quantifiable metabolites (78.3%) may be due to the — RCA assay being less sensitive than the LSC method
- Metabolism of FTC is a minor route for the elimination of FTC; however, three putative metabolites of FTC were detected with structures tentatively identified by —
- FTC metabolites are formed by an oxidation of the thiol moiety to form 3'-sulfoxide diastereomers (designated M1 and M2) and conjugation with glucuronic acid to form the 2'-O-glucuronide (designated M3)

Pharmacokinetics of Intracellular (PBMCs) FTC-5'-TP (by — Analysis)

Table 6 below summarizes the mean PK parameter estimates for intracellular (PBMC) FTC-5'-TP

Table 6. Summary Statistics of PK Parameter Estimates of Intracellular FTC-5'-TP on Day 11 (Steady State)

Statistic	$C_{max,ss}$ (pmoles/10^6 cells)	$t_{max,ss}$ (hr)	$C_{min,ss}$ (pmoles/10^6 cells)	AUCτ (pmoles·hr/10^6 cells)	AUC_{0-t} (pmoles·hr/10^6 cells)	t½ (hr)
Mean	2.34	12.0	0.506	31.24	63.35	39.4
%CV	35	0	40	33	35	28

- The peak FTC-5'-TP concentrations at steady state were similar as those seen in a previous study in HIV-infected subjects (Study FTC-101)

Total ^{14}C-Radioactivity Concentrations in Semen on Day 11 (by LSC)

- Semen ^{14}C-radioactivity concentrations averaged 5.21 µg equiv./mL, which is almost identical to the mean FTC concentrations in semen determined by — analysis
- This indicates unchanged FTC is the primary and possibly the only measurable compound derived from ^{14}C-FTC in semen

- The mean semen to plasma ^{14}C-radioactivity concentration ratio was 3.63 (range: ———)
- The mean semen to blood ^{14}C-radioactivity concentration ratio was 3.98 (range: ———)

Conclusions

- FTC is rapidly and extensively absorbed following oral administration. At least 86% of an oral dose of FTC was absorbed.
- Unchanged FTC is the predominate quantifiable compound in plasma following oral administration.
- Complete recovery of a single ^{14}C-FTC dose in urine (approximately 86%) and feces (approximately 14%) occurs within 7-days.
- Renal excretion (glomerular filtration along with tubular secretion) is the primary elimination route of FTC in plasma
- Approximately 65-70% of an oral FTC dose is excreted in urine as unchanged parent drug. The clinically relevant half-life of FTC is 10 hours.
- Metabolism is a minor elimination pathway for FTC since only 13% of the dose was recovered in urine as 3 putative metabolites. The minor metabolism of FTC would likely present little potential for metabolic drug interactions between FTC and other concurrent drugs. It is still necessary to understand the metabolic pathway of FTC. Therefore, a Phase IV commitment to study the metabolism of FTC will be recommended to the applicant.
- Unchanged FTC achieves semen to plasma concentration ratio of approximately 4
- FTC disposition follows linear, first-order kinetics, with steady-state plasma concentration-time profiles predictable based on a single-dose data.
- Steady state trough plasma FTC concentrations following a 200-mg QD dose averaged 0.07 μg/mL, 5-fold higher than the mean *in vitro* IC_{90} value for anti-HIV activity of FTC.

Protein Binding Study (PDM-037)

Study Rationale

This study was designed to determine the extent of binding of emtricitabine (FTC) to proteins in human, monkey, mouse, and rabbit plasma at concentrations relevant to preclinical toxicology and pharmacology studies and expected concentrations in man.

Study Design

The binding of FTC to human, monkey, mouse, and rabbit plasma proteins was determined over the concentration range of 0.0020 -200 μg/mL by equilibrium dialysis at 37° C.

GLP

This was a Category I study to be conducted in compliance with FDA Good Laboratory Practice (GLP) regulations as set forth in part 58 of Title 21, in the Code of Federal Regulations (CFR).

Test Compound
^{3}H-FTC (Batch UAD) - radiochemical purity and specific activity were 97% and 2.6 Ci/mmol, respectively.

Unlabeled FTC (Batch UM) - purity was > 97% by ——

Human Subjects
Four healthy —— employees (2 female and 2 male) were enrolled into the study after an overnight fast. The plasma from these individuals was pooled for use in this study.

Results
The mean percentage bound for all species studied was less than or equal to 3.6%, with no indication of concentration dependency. Human protein bound percentages over the studied concentration range of 0.0020 - 200 μg/mL are listed below.

Spike Concentration

μg/mL	μM	% Binding to Human Plasma Proteins
0.020	0.081	3.3
0.101	0.409	0.8
0.501	2.03	2.7
2.51	10.2	2.2
10.0	40.4	3.4
49.9	202	2.0
200	808	0.0

Conclusion
- The binding of FTC to plasma proteins was found to be extremely low in all species studied, including human
- The mean percentage bound for all species studied was less than or equal to 3.6%, with no indication of concentration dependency

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6.1.2 Pharmacokinetic & Pharmacodynamic Studies

Dose Escalation and Pharmacodynamic Study (FTC-101)

Study Rationale
In a previous single-dose clinical study (Study 143-001), emtricitabine (FTC) was administered to HIV-1 infected subjects in doses ranging from 100-mg to 1200-mg. These results demonstrated FTC disposition followed linear first order kinetics. Study FTC-101 was designed to assess the safety, tolerability, pharmacokinetics, and antiviral activity of different dosing regimens of FTC monotherapy in HIV-infected subjects and to help select a dosing regimen to study in future Phase II/III studies.