Study Objectives

Primary-

- To evaluate the safety, tolerance, and pharmacokinetics of multiple, repeat doses of FTC at different dosages

Secondary-

- To evaluate preliminary data on the antiviral activity of FTC as a monotherapy and to correlate this activity with pharmacokinetic parameters

Study Population and Demographics

Forty-one subjects were enrolled at six study sites (n =9 for the 25-mg BID cohort and n = 8 for the other 4 cohorts). Table 1 summarizes the demographic data of patients in each dose cohort.

Table 1. Summary of Demographic Data of Patients in Each Dose Cohort Reported as Mean (range)

Demographics	25-mg BID (n = 9)	100-mg BID (n = 8)	200-mg BID (n = 8)	100-mg QD (n = 8)	200-mg QD (n = 8)
Sex	9 M, 0 F	7 M, 1 F	6 M, 2 F	6 M, 2 F	8 M, 0 F
Ethic Origin	7 Caucasian 2 African	3 Caucasian 3 African 2 Hispanic	2 Caucasian 6 African	4 Caucasian 3 African 1 Asian	5 Caucasian 3 African
Age (yr)	35 (28-50)	40 (27- 59)	33 (25- 41)	37 (27 - 48)	37 (29 - 42)
Weight (kg)	81.0 (61.2 - 94.3)	71.2 (52.2 - 93.0)	79.5 (57.1 - 116.3)	78.7 (59.0 - 115.7)	76.5 (64.0 - 96.6)
Est. CL_{cr} (mL/min/1.73 m^2)	106	101	118	107	114

Estimated CL_{cr} = creatinine clearance determined by Cockcroft Gault method and normalized to 1.73 m^2 body surface area.

Pharmacokinetic (PK) Evaluation

The overall PK evaluation plan was to assess the plasma FTC and intracellular (PBMC) FTC-Tri-Phosphate (FTC-TP) PK over a 12-hour post-dose interval on Day 1 and at steady state (Day 10 for plasma and Day 12 for intracellular).

Day 1

- Plasma samples to determine the FTC plasma concentrations were obtained at pre-dose and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12-hour post-dose
- Blood samples to harvest PBMCs were collected just prior to dose and at 1, 3, 6, 9, and 12 hours post-dose.

Days 5, 8, 10, and 12

- Trough concentrations were collected just prior to morning dose on these days.

Day 10

- Plasma samples to determine the FTC plasma concentrations were obtained at pre-dose and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12-hour post-dose.
- Urine samples were collected over the 12-hour post-dose interval following administration of the morning dose.

Day 12

- Blood samples to harvest PBMCs were collected just prior to dose and at 1 and 4 hours after the morning dose.

PK Analysis

Plasma FTC concentration-time data were analyzed by noncompartmental methods using WinNonLin, Professional version 3.1.

- **Day 1:** Plasma FTC concentration-time data following the first dose of FTC were used to calculate the following PK parameters: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_z, $t½$, CL/F, and V_z/F
- **Day 10:** Plasma FTC concentration-time data following multiple doses of FTC were used to calculate the following PK parameters: $C_{max,ss}$, $t_{max,ss}$, $AUC\tau$, λ_z, $t½$, CL_{ss}/F, and $V_{z,ss}/F$. The 24-hour post-dose FTC concentrations for the QD dose cohorts was determined by averaging the pre-dose (trough) plasma concentrations determined on Days 5, 8, 10, and 12 for each subject.
- Urinary excretion data were analyzed to determine the amount of FTC excreted (A_e) and the % of dose excreted as FTC in urine over the 12-hour post-dose interval at steady state

Assay/Analytical Method

A validated [redacted], bioanalytical method was used to determine FTC concentrations in plasma and urine. Triangle Pharmaceuticals, Inc., Durham, NC, validated the method.

Plasma

Plasma samples were analyzed with calibration standards at 10 concentrations and QC samples at 4 concentrations. There were a total of 7 analytical runs. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 6.85 to 9.80% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -1.3% to 2.0% for the human plasma assay.

Urine

Study urine samples were analyzed in a single analytical run with calibration standards at 6 concentrations and QC samples at 5 concentrations. Correlation coefficients were all greater than 0.99. Inter-day precision was not determined. Inter-day accuracy, expressed as %bias, ranged from -2.1% to 5.3% for the urine assay.

Other Statistical Analyses

- Dose Proportionality-Power Model
- Dose-Response : simple E_{max} model

FTC-101 Results

PK Results-

Tables 2 and 3 contain the summary PK parameter estimates for Day 1 and Day 10.

Table 2. Arithmetic Mean Summary Statistics for FTC PK Parameter Estimates Following Single Dose Administration (Day 1) by Dose Cohort and Dose

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	AUC_{0-t} (µg·h/mL)	$AUC_{0-\infty}$ (µg·h/mL)	$t_{1/2}$ (h)	CL/F (mL/min)
25-mg BID (n = 9)	Mean %CV	0.15 24	1.60 53	0.60 21	0.68 21	3.61 21	638 22
100-mg BID (n = 8)	Mean %CV	0.90 37	2.41 52	3.68 27	4.14 35	3.26 23	440 29
200-mg BID (n = 8)	Mean %CV	1.63 21	1.14 34	5.99 16	6.37 16	2.83 10	535 15
100-mg QD (n = 8)	Mean %CV	0.98 43	1.54 45	3.16 33	3.42 32	3.48 24	537 35
200-mg QD (n = 8)	Mean %CV	1.54 38	2.25 46	6.47 18	7.07 19	2.98 14	489 22
100-mg combined (n = 16)	Mean %CV	0.94 40	1.97 55	3.42 30	3.78 34	3.37 23	489 34
200-mg combined (n = 16)	Mean %CV	1.59 30	1.70 56	6.23 17	6.72 18	2.90 12	512 18

Table 3. Arithmetic Mean Summary Statistics for FTC PK Parameter Estimates 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)	$t_{1/2}$ (h)	CL_{ss}/F (mL/min)
25-mg BID (n = 9)	Mean %CV	0.23 30	1.39 39	0.029 32	0.99 17	5.26 8	430 17
100-mg BID (n = 8)	Mean %CV	1.15 19	1.69 63	0.148 68	5.39 35	4.25 15	339 30
200-mg BID (n = 8)	Mean %CV	2.05 34	1.23 28	0.171 23	8.47 26	3.59 16	415 26
100-mg QD (n = 8)	Mean %CV	0.90 20	1.21 23	0.035 50	4.10 22	9.49 21	423 21
200-mg QD (n = 8)	Mean %CV	1.72 53	2.00 48	0.047 24	8.00 15	8.24 31	425 15

- For the FTC BID cohorts (i.e., 25-mg, 100-mg, and 200-mg BID) the plasma C_{max} and AUC of FTC accumulated (R) 30-50% higher on average after multiple dosing to steady state
- For the QD dose cohorts, C_{max} had no accumulation in the 100-mg QD cohort, but 1.12 fold higher in the 200-mg QD cohort at steady state; however, AUC values accumulated to 1.2 and 1.3 fold higher on Day 10 in the 100-mg and 200-mg QD cohorts, respectively
- The dose-normalized AUCτ (or AUC_{0-24}) and C_{max} values were very similar between dose cohorts.

Reviewer Comment: Dose proportionality was further evaluated by statistical analysis and will be discussed later.

Urine Results

Table 4 provides a summary of the urinary recovery and renal clearance (CL_R) data for each dose cohort. These data were collected for 12 hours post drug administration on Day 10.

Table 4. Summary of Urinary Recovery and CL_R Data for Each Dose Cohort on Day 10 Reported as Mean (range)

Demographics	25-mg BID n = 9	100-mg BID n = 8	200-mg BID n = 8	100-mg QD n = 8	200-mg n = 8
% Dose Excreted as FTC	59.5	72.8	74.2	67.6	65.2
CL_R (mL/min)	253	244	334	305	319
CL_{cr} (mL/min)	123	109	135	123	128

Estimated CL_{cr} = creatinine clearance determined by Cockcroft Gault method

Reviewer Comment: These results are very similar to other urine data reported in other FTC studies.

Dose Proportionality Results

Two analyses were conducted to assess dose proportionality. The primary assessment was performed using a power model that became a linear model after log transformation, log(y) = a + b x log(dose). The second analysis of dose proportionality was performed using analysis of variance (ANOVA). Dose proportionality was concluded if the 90% CI of the slope from the power model was within a pre-specified acceptance range of 30% around unity. This 30% pre-specified range was selected based on the wide dose range evaluated. The PK parameters studied for dose proportionality are C_{max} and AUC for Day 1 PK and $C_{max,ss}$, $C_{min,ss}$, and AUCτ for Day 10 PK parameters.

Day 1-single dose/dose proportionality

- The 90% CI for the slope was within 20% of unity for AUC_{0-inf} and within 30% of unity for C_{max}
- The ANOVA results supported this finding, except that the 25-mg dose had lower than dose proportional values

Day 10-multiple dose/dose proportionality

- The 90% CI for the slope was within 20% of unity for AUCτ and $C_{min,ss}$ and within 30% of unity for $C_{max,ss}$

- The ANOVA results supported this finding, except that it revealed the 100-mg BID dose had higher than dose proportional values

Intracellular Concentrations of FTC-TP Results
Day 1

- FTC-TP is readily formed in PBMCs and is measurable at the first sampling time point (1 hour) following the first dose on Day 1
- FTC-TP concentration increased in a dose-related fashion and the median FTC-TP concentrations peaked at 1.6 pmole/10^6 cells around the 6 hour post dose time point for the 100-mg and 200-mg single dose (FTC-TP peaked between 3-6 hours for all groups)

Day 12

- FTC-TP concentration increased in a dose-related fashion and reached an apparent plateau level of ~ 4 pmole/10^6 cells for the median FTC-TP concentrations at FTC daily doses of 200-mg or greater
- The FTC-TP concentration vs. dose curves are consistent with the saturable enzyme kinetics curve

Reviewer Comment: The Applicant states due to small sample size and relatively larger variability in cell counts and FTC-TP measurements, the median value was used as the primary summary statistic.

PK-Pharmacodynamic Correlation Results

- All doses studied demonstrated an antiviral response
- There was a trend for less antiviral response at doses 50-mg QD to 100-mg QD FTC per day compared to > 200-mg FTC per day
- A median viral load reduction of 1.9 $\log_{10}$ was seen with daily doses of 200-mg or more at Day 15 (ranged 1.7 to 1.9 $\log_{10}$) versus 1.3 to 1.5 $\log_{10}$ at 50-mg and 100-mg FTC doses per day, respectively
- Statistical analyses of plasma HIV-1 RNA levels demonstrated a dose-response relationship, with maximal HIV-RNA suppression occurring at the 200-mg QD and 200-mg BID doses.
- Using a simple E_{max} model, the dose-response relationship for the anti-HIV activity of FTC was measured by analyzing the antiviral activity expressed as the average AUC minus baseline (AAUCMB) over the Days 1 to 15

The parameter estimates determined by the model are summarized in Table 5.

Table 5. PK Parameter Estimates

Parameter	Estimate	%CV in Estimate
E_{max}	1.34 $\log_{10}$	4.2%
E_{50}	12.7-mg	17%
Correlation Coefficient (r)	0.89	n/a

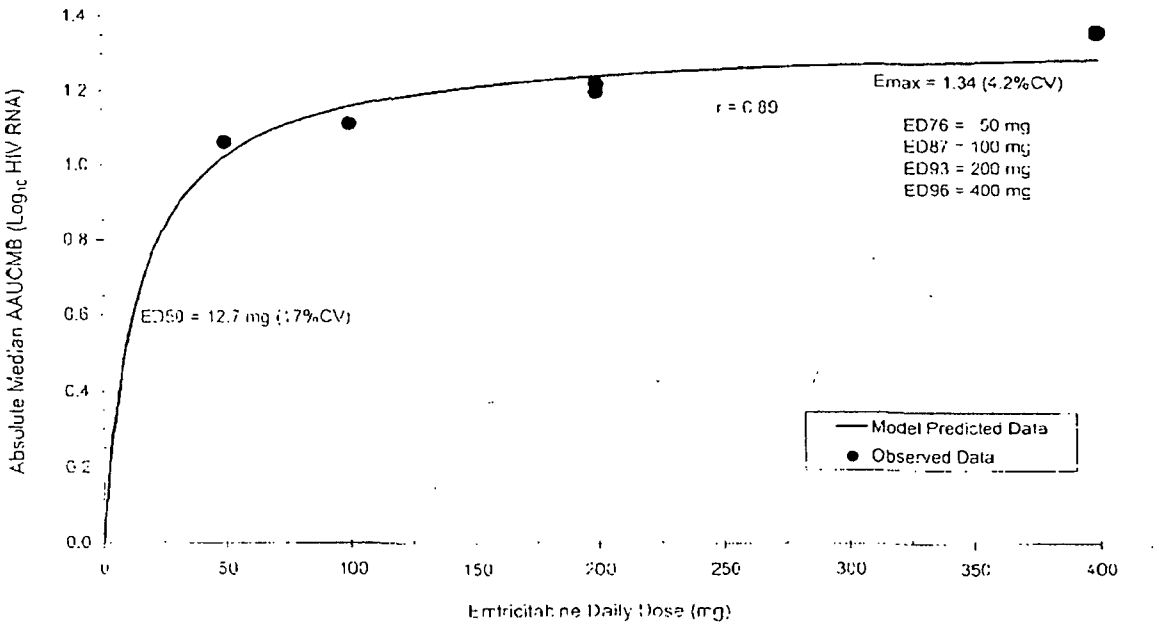
PK-Pharmacodynamic Correlation Results Continued

Table 6 summarizes the antiviral effect of FTC for each dose study based on the E_{max} and ED_{50} estimates. Figure 1 represents the dose-response relationship of anti-HIV activity of FTC, as determined by the pharmacological simple E_{max} model.

Table 6. Antiviral Effect of FTC Based on the E_{max} and ED_{50} Estimates Expressed as Percent of the Maximal Activity

FTC Total Daily Dose	Percent of Maximal Activity
50-mg	76%
100-mg	87%
200-mg	93%
400-mg	96%

Figure 1. Dose-Response Relationship of Anti-HIV Activity of FTC: Plots of Log_{10} HIV-1 RNA AAUCMB versus FTC Daily Activity



Reviewer Comment: This model demonstrates antiviral activity of FTC dose reaches a plateau as the dose increases. By doubling the daily dose of FTC (200-mg versus 400-mg daily), a net gain of only 3% more antiviral activity is achieved. The maximal antiviral activity is estimated to be 1.34 log_{10}. At a 200-mg dose, the observed median AAUCMB is 1.22 log_{10}, approaching the maximal activity estimate. This provides validation for the Applicant's therapeutic FTC dose selection of 200-mg QD.

Conclusion

- FTC reaches peak plasma concentration between 1.5 to 2 hours post-dose (t_{max})
- 60-70% of an oral dose of FTC is recovered in the urine as unchanged FTC
- Plasma FTC concentrations achieved levels well above the *in vitro* IC_{90} (μg/mL) over a 24-hour period for all dosing regimens studied in FTC-101

- Plasma concentrations of FTC increased in a dose proportional manner following both single-dose and multiple dose administration
- Plasma elimination half-life is approximately 9 hours
- CL_R of FTC ranged from 250-330 mL/min across all dosing groups, which indicates that FTC is actively secreted by renal tubules
- FTC demonstrates linear PK over the studied dosing ranges and steady-state concentrations were predictable based on single-dose PK
- The long plasma half-life and level of exposures achieved support QD dosing
- FTC 200-mg QD dose achieved 93% of maximal antiviral activity with little additional activity observed as dose doubles

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Pharmacokinetic Sub-Study (FTC-303)

Study Rationale

FTC-303 sub-study was designed to confirm the pharmacokinetic (PK) profile of emtricitabine (FTC) at steady-state over a 24-hour dosing interval.

Study Objectives

- To confirm the PK profile of FTC at steady-state conditions

Study Population and Demographics

A total of 13 subjects were recruited from the FTC treatment arm of Study FTC-303. A total of 12 subjects had evaluable PK data. Patient #114 was excluded because the patient misunderstood the instructions and took the their morning dose of FTC prior to the first blood draw. Table 1 summarizes the demographic profiles of the 12 study subjects.

Table 1. FTC-303 Sub-Study Subject Demographics

Patient ID	Visit Week	Sex	Ethnicity	Age (yr.)	Wt. (kg)	BSA (m^2)	CL_{cr} (mL/min)
43	30	F	Caucasian	32	64.50	1.75	102.8
127	38	F	Caucasian	32	70.50	1.88	128.4
128	29	F	Caucasian	50	68.60	1.84	81.0
145	23	F	Caucasian	30	72.30	1.89	104.3
147	23	F	Caucasian	28	75.0	1.95	110.2
264	29	F	Caucasian	34	705.50	1.88	88.2
304	4	M	Black	31	97.70	2.12	184.9
534	20	F	Hispanic	40	69.50	1.76	102.6
607	16	F	Caucasian	42	79.00	1.92	101.6
611	16	F	Caucasian	61	92.10	2.13	122.7
615	16	F	Caucasian	40	67.10	1.79	49.5
632	4	F	Caucasian	41	81.6	2.06	86.7
Mean (%CV)	-	-	-	38 (25)	75.70 (14)	1.91 (7)	105.2 (31)

PK Sampling Procedures

Blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.

PK Analysis

- Steady-state plasma FTC concentration versus time data for each subject were analyzed by noncompartmental methods using WinNonlin, Professional (version 3.1) and used to calculate $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, AUC_{τ}, λ_z, t½, and CL_{ss}/F

Assay/Analytical Method

A validated [redacted] bioanalytical method was used to determine FTC concentrations in plasma. Triangle Pharmaceuticals, Inc., Durham, NC, validated the method. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 6.24 to 11.23% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -5.8% to 14.0% for the human plasma assay.

Study Drug

- Emtricitabine: 200-mg QD administered in combination with other antiretrovirals including NRTIs, NNRTIs, and PI.
- The study subjects background regimen were administered 2 hours after the administration of FTC on the PK sampling day.

FTC-303 PK Results

Table 2 below summarizes the descriptive statistics for FTC PK parameter estimates determined at steady state.

Table 2. Descriptive Statistics for FTC PK Parameter Estimates Determined at Steady-State

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)

- The mean trough concentration was 8-fold (range 3 to 20-fold) higher than the mean *in vitro* IC_{90}

Conclusion

- FTC demonstrated PK characteristics consistent with those seen in previous PK studies

6.1.3 Bioavailability and Bioequivalence Studies

Absolute Bioavailability Study (FTC-110)

Study Objectives

- To determine the relative bioavailability (BA) of oral emtricitabine (FTC), administered as the 200-mg oral capsule formulation, when compared to the oral solution formulation of FTC
- To determine the absolute BA of oral FTC, administered as the 200-mg capsule formulation, when compared to an intravenous (IV) dose of FTC
- To determine the absolute BA of oral FTC, administered as a solution formulation, when compared to an IV dose of FTC

Study Design

This was an open-label, randomized, three-way crossover study to evaluate the single-dose pharmacokinetics (PK) of FTC when administered as three different formulations: oral solution, oral capsule, and IV. A ≥ 1-week washout interval separated each treatment period.

Study Subjects Demographics

Twelve subjects were enrolled and completed the study. The mean age for study subjects was 32 years (range 21-44) with 11 Caucasian/1 African American subjects. Seven subjects were male and 5 subjects were female.

FTC Formulations

A description of FTC formulations evaluated in this study is provided in Table 1.

Table 1. FTC Formulations Administered in Study FTC-110

Formulation	Theoretical Batch Size	Lot Number/Expiration Date
200-mg FTC Oral Capsule	[redacted]	TP-0006-00205/November 2001
10-mg/mL FTC Oral Solution	[redacted]	TP-0006-00211/July 2001
10-mg/mL FTC IV Solution	[redacted]	TP-0006-00093/ May 2001

Study Treatments

- Treatment A: one 200-mg FTC oral capsule
- Treatment B: 20 mL of a cotton candy-flavored 10-mg/mL FTC oral solution
- Treatment C: 20 mL of a 10-mg/mL FTC IV solution. The IV solution was diluted in 0.9% Sodium Chloride for Injection, USP to a total volume of 50 mL and administered by a constant infusion over a 1-hour period at a constant rate of 0.83 mL/min (3.32 mg/mL)

PK Sampling Scheme

Blood-

- No specific time points for sample collection were provided in the study report for the PK sampling. The report includes a general comment stating blood samples were collected at pre-dose and then at predetermined intervals up to 48 hours post-dose for all subjects.

Urine-

- During each period, urine was collected from each subject starting prior to dosing and continuing over predetermined intervals at 0-6, 6-12, 12-24, and 24-48 hours post-dose

PK Analysis

- Plasma FTC concentration-time data for each subject were analyzed by noncompartmental methods, using WinNonLin, Professional version 3.1.
- The following PK parameters were calculated: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t½$, $AUC_{0-\infty}$, CL (total body clearance), CL/F (apparent total body clearance), V_z (volume of distribution), V_z/F (apparent volume of distribution), and A_e (amount of FTC excreted in urine)
- All PK parameters except for t_{max} were log transformed before statistical analyses. SAS, version 8.1 was used to compare Treatment A/Treatment B, Treatment A/Treatment C, and Treatment B/Treatment C
- 90% CI were calculated for each parameter and the geometric least-squares mean (GLS) ratios were used and reported as the primary estimates of relative or absolute BA

Assay/Analytical Method

A validated [redacted] bioanalytical method was used to determine FTC concentrations in plasma and urine. Triangle Pharmaceuticals, Inc., Durham, NC, validated the method.

Plasma

Study plasma samples were analyzed with up to 10 calibration standards and a minimum of 12 QC samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 8.05 to 20.18% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -3.6% to 1.2% for the human plasma assay.

Urine

Study urine samples were analyzed with up to 8 calibration standards and a minimum of 8 QC samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 5.39% to 13.44% for the human urine assay. Inter-day accuracy, expressed as %bias, ranged from -6.1% to 4.0% for the human urine assay.

FTC-110 Study Results

Table 2 provides the FTC PK arithmetic mean parameter estimates by treatment and Table 3 provides the BA statistical results of treatment comparisons.

Table 2. Summary FTC Arithmetic PK Parameter Estimates Reported as Mean (%CV) from Study FTC-110

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	AUC_{0-t} (µg•h/mL)	AUC_{0-t} (µg•h/mL)	$t_{½}$ (h)	V_z/F (L)	CL/F (mL/min)
200-mg Capsule n = 12	Mean	2.24	1.21	10.20	10.37	8.89	256	330
	%CV	19	32	17	17	12	24	16
	Mean							
	%CV							
200-mg IV n = 12	Mean	3.97	1.00	11.07	11.21	9.04	242	307
	%CV	16	8	19	19	10	23	19

Table 3. Summary of FTC BA Estimates for Study FTC-110-Results of Statistical Analysis

Statistic	Treatment Comparison		
	Capsule/Solution	Capsule/IV	
$AUC_{0-\infty}$ (µg•h/mL) GLS Mean Ratio 90% CI	1.244 1.166-1.327	0.929 0.781-0.990	
AUC_{0-t} (µg•h/mL) GLS Mean Ratio 90% CI	1.279 1.198-1.365	0.924 0.866-0.987	
C_{max} (µg/mL) GLS Mean Ratio 90% CI	1.533 1.418-1.657	0.561 0.519-0.607	

Reviewer Comment: Since the Applicant has withdrawn ,
I will only comment on the capsule/IV solution comparison.

- The absolute BA for FTC 200-mg capsule is 93%, which is an indication of nearly complete absorption for the FTC capsule and negligible first-pass metabolism for FTC
- FTC C_{max} for the 200-mg capsule formulation was approximately 60% of the IV solution C_{max} value; however, both t_{max} and C_{max} values for the IV formulation are dependent on the rate and duration of the IV infusion

Urinary Excretion Data

All 12 subjects had normal renal function, with an estimated CL_{cr} values > 80 mL/min (range 85-154 mL/min). Table 4 summarizes the FTC urinary excretion data.

Table 4. Summary Statistics of FTC Urinary Excretion Data

Urinary Excretion Parameter	Statistic	FTC Treatment Group	
		200-mg Capsule	200-mg IV Infusion
Total % Dose Excreted as FTC	Mean %CV	68.62 20	72.90 6
Average CL_R (mL/min)	Mean %CV	227.9 22	227.3 21
Ratio of CL_R:CL (IV) or CL_R:CL/F (oral)	Mean %CV	0.698 20	0.738 6

- CL_R values were similar between treatment groups
- CL_R values were consistently higher than CL_{cr}, which is indicative of a net renal tubular secretion of FTC
- FTC is primarily eliminated from plasma as unchanged FTC (60-70% of an oral dose)

Reviewer Comment: These findings are consistent with other urinary excretion data collected in other FTC studies.

Conclusion

- The absolute BA of the 200-mg FTC capsule formulation is 93%
-

Pivotal Bioequivalence Study (FTC-111)

Background

Two bioequivalence (BE) studies (FTC-109 and FTC-111) were performed to compare the bioavailability (BA) of emtricitabine (FTC) between the 100-mg capsule formulation used in early Phase I clinical studies and the 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 assesses the BE of the 200-mg capsule formulation intended for marketing as 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.

Study Design
An open-label, randomized, 3-way crossover study that evaluated the single-dose pharmacokinetics of FTC administered as two oral capsule formulations under either fasting conditions or with a high-fat meal (for the 200-mg capsule only) in 24 healthy volunteers. There were 7 males and 17 females enrolled with a mean age of 24 years [ranging from 20 to 33 years of age].

Subjects received the following three treatments in a randomized fashion, with treatments separated by a one-week washout period.

Study Treatments
- Treatment A: 2 x 100-mg emtricitabine capsules, administered under fasting conditions
- Treatment B: 1 x 200-mg emtricitabine capsule, administered under fasting conditions
- Treatment C: 1 x 200-mg emtricitabine capsule, administered 5-minutes after completing a standard high-fat meal

Test and Reference Product
- Test Product: 200-mg emtricitabine capsule, Lot # TP-0006-00205, Batch Size:
- Reference Product: 100-mg emtricitabine capsule, Lot # TP-0006-00120, Batch Size:

Standard High-Fat Meal Composition

Carbohydrate	58 g	232 kcal	971 kJ	21.4%
Protein	33 g	132 kcal	552 kJ	15.5%
Fat	67 g	603 kcal	2523 kJ	63.1%

Pharmacokinetic Sampling
Serial blood samples for the determination of plasma FTC concentrations were collected at pre-dose (time 0) and then 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose.

FTC-111 Assay Validation
A validated bioanalytical method (Method #6647, version 3) was used to assay FTC plasma samples. The assay is acceptable. The assay characteristics for FTC-111 are listed below.

Parameter	Observation
Linear Range	ng/mL
LLOQ	ng/mL
Stability (freeze-thaw)	Stable for 320 days when frozen at -80° C
Specificity	
QC sample concentrations	5, 25, 1000, and 4000-ng/mL

Intra-day Accuracy N = 5	Intra-day Precision N = 5	Inter-day Accuracy N = 15	Inter-day Precision N = 15

Assay precision and accuracy were evaluated using 3 analytical runs, each containing quality control (QC) samples (n = 4) in replicates of 5.

Pharmacokinetic Data Analysis

All pharmacokinetic parameters were analyzed using analysis of variance (ANOVA). The primary analysis was based on log transformed pharmacokinetic parameters except for t_{max}. SAS™ (Version 6.12) PROC MIXED was used to compare treatments.

Study Results

The summary statistics of FTC pharmacokinetic parameters are listed in Table 1.

Table 1. 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)	t½ (h)	CL/F mL/min	V_z/F (L)
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 below in Table 2.

Table 2. Statistical Analysis of FTC Pharmacokinetic Parameters

Statistic	GLS Mean 100-mg	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)

Assessment/Conclusion

- FTC-111 data demonstrate the 200-mg capsule (to-be marketed formulation) is BE to the 100-mg capsule used in pivotal clinical trials
- 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 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. The total exposure (AUC) is a better indicator for intracellular concentrations versus C_{max}. Therefore, these differences do not appear to be of clinical significance. FTC was administered without regard to food timing in clinical trials.
- It is safe to conclude FTC can be administered with or without food

6.1.4 Drug-Drug Interaction Studies

Emtricitabine, Zidovudine, and Stavudine Interaction (FTC-103)

Study Rationale

Retrovir™ (ZDV) and Zerit™ (d4T) are approved nucleoside reverse transcriptase inhibitors (NRTIs) for the treatment of HIV-1 infection when used in combination with other antiretroviral agents. It is expected that emtricitabine (FTC) will be used in combination with both ZDV and d4T; therefore, the applicant evaluated the potential for drug-drug interactions between FTC and the two NRTIs.

Study Objectives

- To evaluate the potential pharmacokinetic (PK) interactions of FTC with ZDV or d4T and to assess the safety of the two-drug combinations in healthy male and female volunteers

Study Design

This was a single-center, open-label, single-dose, randomized, three-period crossover study. Eligible subjects were assigned to one of two treatment cohorts (n = 6 per cohort), then randomized into one of three dosing sequences (n = 2 per sequence). Dosing periods were separated by a 36-hour washout period.

Study Subjects Demographics

A total of 12 healthy volunteers were planned for the study; 13 subjects were enrolled and 12 subjects completed all scheduled dosing and study procedures. One subject in Cohort 2 discontinued early due to an adverse event (ADE) that occurred on Day 2 following FTC 200-mg/d4T 40-mg dosing. Table 1 provides the demographic summary for subjects enrolled into FTC-103.

Table 1. Summary of Subject Demographics Enrolled in FTC-103

Parameter	Statistic	Cohort 1 (FTC/ZDV) N = 6	Cohort 2 (FTC/d4T) N = 7
Age (yr)	Mean (range)	28.5 (21.0 - 45.0)	24.6 (18.0 - 34.0)
Weight (kg)	Mean (range)	72.3 (64.5 - 82.7)	74.8 (57.3 - 92.7)
Est. CL_{cr} (mL/min)	Mean (range)	114.4	115.2
Sex	-	Male 5/Female 1	Male 6/Female 1
Race*	-	AA-2/C-3/H-1	AA-4/A-1/C-2

*AA-African American/C-Caucasian/H-Hispanic/A-Asian

Study Drugs/Doses/Mode of Administration/Lot Numbers

- FTC- 2 x 100-mg oral capsule, Batch No. TP-0006/96/R, Lot # 26295, Batch size:
- Retrovir™- 3 x 100-mg oral capsule, Lot # 7ZP1683
- Zerit™- 1 x 40-mg oral capsule, Lot # MMH03 (all subjects enrolled into Cohort 2 ≥ 60 kg)

Cohort 1
Received the following treatments in a randomized fashion on Days 1, 3, and 5:
- Single oral dose of FTC 200-mg
- Single oral dose of ZDV 300-mg
- Single oral dose of FTC 200-mg + ZDV 300-mg

Cohort 2
Received the following treatments in a randomized fashion on Days 1, 3, and 5:
- Single oral dose of FTC 200-mg
- Single oral dose of d4T 40-mg
- Single oral dose of FTC 200-mg + d4T 40-mg

PK Sampling Scheme
Full PK profile evaluations were conducted for all three drugs. Blood samples for the determination of FTC, ZDV, and d4T concentrations were collected pre-dose and then at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, and 36 hours post-dose on Days 1, 3, and 5.

PK Analysis/Statistical Analysis
- Plasma FTC, ZDV, and d4T concentration-time data alone were analyzed by noncompartmental methods
- The following PK parameters were determined: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t½$, $AUC_{0-\infty}$, CL/F, V_z/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, version 6.12
- The applicant's criteria for a lack of clinically significant difference between the test and reference regimens were a 90% CI for the ratio of $AUC_{0-\infty}$ and C_{max} 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, ZDV, and d4T in human plasma have been validated according to Triangle Pharmaceutical applicable standard operating procedures (SOP). A
bioanalytical method was used to determine FTC, ZDV, and d4T concentrations in plasma.

FTC-
Study plasma samples were analyzed with up to 7 calibration standards and a minimum of 1QC per 12 samples. Correlation coefficients were all greater than — Inter-day precision, expressed as %CV, ranged from 4.77% to 12.12% for the human plasma assay. Inter-day accuracy, expressed as % bias, ranged from -2.0% to 4.8% for the human plasma assay. The lower limit of quantitation (LLOQ) of FTC for the study samples was ~ ng/mL.

ZDV-
Study plasma samples were analyzed with up to 7 calibration standards and a minimum of 1QC per 12 samples. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 6.77% to 10.28% for the human plasma assay. Inter-day accuracy, expressed as % bias, ranged from -6.2% to 4.4% for the human plasma assay. The LLOQ of ZDV for the study samples was ~ng/mL.

d4T-
Study plasma samples were analyzed with up to 6 calibration standards and a minimum of 1QC per 12 samples. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 6.69% to 13.09% for the human plasma assay. Inter-day accuracy, expressed as % bias, ranged from -1.6% to 6.7% for the human plasma assay. The LLOQ of d4T for the study samples was ~ ng/mL.

FTC-103 Study Results
Cohort 1- FTC & ZDV
Table 2 summarizes the mean (%CV) values for FTC PK parameters when administered alone or in combination with ZDV. Table 3 summarizes the statistical analysis of FTC PK parameters when administered alone or in combination with ZDV.

Table 2. Mean (%CV) Values for FTC PK Parameters when Administered Alone or in Combination with ZDV (N=6)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)
FTC	Mean	2.45	1.21	9.93	10.37	342	311
	%CV	31	38	16	22	15	31
FTC + ZDV	Mean	2.41	1.08	11.07	9.17	304	242
	%CV	30	43	12	16	11	20

Table 3. Statistical Analysis of FTC PK Parameters (N=6)

PK Parameter	Statistical Value	FTC (reference)	FTC + ZDV (test)	Statistical Analysis	FTC +ZDV / FTC
$AUC_{0-\infty}$ (µg•h/mL)	Geom. Mean	9.83	11.01	GLS Ratio	1.120
				90% CI	1.038, 1.207
C_{max} (µg/mL)	Geom. Mean	2.36	2.33	GLS Ratio	0.991
				90% CI	0.648, 1.516

Reviewer Comment: Although the 90% CI for C_{max} was outside the 80-125% range for geometric least squares mean ratios, the point estimate was near unity (0.991). The small sample size could be responsible for the wide 90% CI for C_{max}. 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}. For these reasons listed, the C_{max} decrease seen with FTC when combined with ZDV will not be clinically significant.

Table 4 summarizes the mean (%CV) values for ZDV PK parameters when administered alone or in combination with FTC. Table 5 summarizes the statistical analysis of ZDV PK parameters when administered alone or in combination with FTC.

Table 4. Mean (%CV) Values for ZDV PK Parameters when Administered Alone or in Combination with FTC (N=6)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	t½ (h)	CL/F (mL/min)	V_z/F (L)
ZDV	Mean	1.48	0.88	2.28	1.14	2267	217
	%CV	47	39	21	27	19	23
ZDV+FTC	Mean	2.42	0.67	2.85	1.32	1783	206
	%CV	42	31	15	14	13	26

Table 5. Statistical Analysis of ZDV PK Parameters (N=6)

PK Parameter	Statistical Value	ZDV (reference)	ZDV + FTC (test)	Statistical Analysis	ZDV + FTC / ZDV
$AUC_{0-\infty}$ (µg•h/mL)	Geom. Mean	2.24	2.83	GLS Ratio	1.261
				90% CI	0.978, 1.626
C_{max} (µg/mL)	Geom. Mean	1.37	2.26	GLS Ratio	1.655
				90% CI	0.982, 2.789

Reviewer Comment: These data show ZDV exposure increased by 26% when combined with FTC. In addition, ZDV C_{max} increased 66% when combined with FTC. These increases could be inflated due to the small sample size.

Other antiretroviral drugs have documented interactions with ZDV (amprenavir increases ZDV AUC and C_{max} by 31% and 40%, and 3TC increases ZDV C_{max} by 39%, respectively) that are not considered clinically significant. Although similar decreases in ZDV CL/F and increases in ZDV AUC are documented, the 66% increase in ZDV C_{max} is larger than other documented increases. This C_{max} increase may be inflated due to the small sample size.

Cohort 2- FTC & d4T

Table 6 summarizes the mean (%CV) values for FTC PK parameters when administered alone or in combination with d4T. Table 7 summarizes the statistical analysis of FTC PK parameters when administered alone or in combination with d4T.

Table 6. Mean (%CV) Values for FTC PK Parameters when Administered Alone or in Combination with d4T (N=6)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	t½ (h)	CL/F (mL/min)	V_z/F (L)
FTC	Mean	2.36	1.21	11.28	8.31	302	219
	%CV	32	27	16	17	17	28
FTC + d4T	Mean	2.47	1.29	11.54	9.67	298	253
	%CV	30	26	19	15	19	32

Table 7. Statistical Analysis of FTC PK Parameters (N=6)

PK Parameter	Statistical Value	FTC (reference)	FTC + d4T (test)	Statistical Analysis	FTC +d4T / FTC
$AUC_{0-\infty}$ (μg•h/mL)	Geom. Mean	11.16	11.37	GLS Ratio 90% CI	1.019 0.939, 1.106
C_{max} (μg/mL)	Geom. Mean	2.28	2.37	GLS Ratio 90% CI	1.042 0.937, 1.159

Reviewer Comment: When FTC and d4T are administered together, there is no change in the $AUC_{0-\infty}$ and C_{max} of FTC. It can be concluded that d4T has no effect on FTC PK.

Table 8 summarizes the mean (%CV) values for d4T PK parameters when administered alone or in combination with FTC. Table 9 summarizes the statistical analysis of d4T PK parameters when administered alone or in combination with FTC.

Table 8. Mean (%CV) Values for d4T PK Parameters when Administered Alone or in Combination with FTC (N=6)

TX	Statistic	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg•h/mL)	t½ (h)	CL/F (mL/min)	V_z/F (L)
d4T	Mean	0.74	0.79	2.00	1.99	344	57
	%CV	18	24	20	36	18	23
d4T+FTC	Mean	0.79	0.75	2.18	2.13	314	58
	%CV	29	30	19	15	16	22

Table 9. Statistical Analysis of d4T PK Parameters (N=6)

PK Parameter	Statistical Value	d4T (reference)	d4T + FTC (test)	Statistical Analysis	d4T + FTC / d4T
$AUC_{0-\infty}$ (μg•h/mL)	Geom. Mean	1.96	2.15	GLS Ratio 90% CI	1.093 0.830, 1.439
C_{max} (μg/mL)	Geom. Mean	0.73	0.77	GLS Ratio 90% CI	1.052 0.952, 1.162

Reviewer Comment: The d4T AUC fell outside the acceptable 90% CI range of 80-125%. The reason for this most likely is due to the small sample size. C_{max} was well within the acceptable range. It can be concluded that FTC has no effect on the PK of d4T.

Conclusions

- Single dose ZDV and d4T had no effect on the PK of FTC.
- Single dose FTC had no clinically significant effect on the PK of d4T.
- Single dose FTC increased the $AUC_{0-\infty}$ and C_{max} of ZDV by 26% and 66%, respectively.
- Exposure and safety data are available for ZDV when dosed at 200-mg 4-6 times per day. These data support the conclusion that the increased ZDV exposures seen in FTC-103 are not clinically significant.
- These ZDV increases are most likely due to a small sample size.
- The applicant conducted an additional FTC + ZDV drug-drug interaction study recently (FTC-115), in which ZDV and FTC were administered in multiple doses and a larger subject pool enrolled. The FTC-115 ZDV exposures observed when combined with FTC were much less than the exposures observed for ZDV in FTC-103. Since these data will be forthcoming in a final study report soon after FTC approval date, the earlier study results were not included in the original FTC label.

Emtricitabine and Indinavir Interaction Study (FTC-104)

Study Rationale

Emtricitabine (FTC), if approved, will be used in combination with other antiretroviral agents. Ideally the drugs that will be combined to treat HIV infected subjects should not alter the pharmacokinetics (PK) of one another. Therefore, it is important to prospectively conduct studies to explore the potential for drug-drug interactions. FTC-104 is designed to evaluate the potential for an interaction with drugs that are primarily metabolized by the liver.

Reviewer Comment: This study report will only include data for FTC and indinavir (IDV).

Study Objectives

Primary-

- To determine whether FTC affects the PK of IDV
- To determine whether IDV affects the PK of FTC

Secondary-

- To determine the safety of administration of single doses of FTC with a single dose of IDV

Study Design

This was a single-center, open-label, three-period, crossover study in healthy male and female subjects. A total of 24 subjects were recruited and enrolled. Subjects were randomly assigned to one of two cohorts (12 subjects per cohort), then randomized to one of six treatment sequences. A 2-day washout period separated each treatment.

Study Subjects Demographics

Of the 12 healthy volunteers in Cohort 1, the majority were male (10/12, 83%) and most were Caucasian (9/12, 75%). The average age and weight of the subjects in Cohort 1 were 28 years (range, 18 to 42 years) and 76.6 kg (range, 61.6-88.5 kg), respectively. These subjects received the IDV and FTC combination.

The majority of subjects in Cohort 2 were male (8/12, 67%) and Caucasian (9/12, 75%). The average age and weight for subjects in Cohort 2 were 35 years (range, 25-44 years) and 70.8 kg (range, 57.3-83.2 kg), respectively. These subjects received the MK-442 and FTC combination.

Study Drugs/Lot Numbers/Batch Size

- FTC- 100-mg capsule/Lot #P-0006-96-BB/Theoretical Batch Size-
- IDV- CRIXIVAN™ (Merck) 400-mg capsule/Lot #E7199

Treatment Regimens

- FTC: 2 x 100-mg FTC capsules
- IDV: 2 x 400-mg IDV capsules
- FTC + IDV: 2 x 100-mg FTC capsules + 2 x 400-mg IDV capsules

PK Sampling Scheme to Measure FTC & IDV Concentrations
Plasma-
On study Days 1, 3, and 5 blood samples for determination of FTC and IDV plasma, concentrations were collected at pre-dose and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours post-dose administration.

PK Analysis/Statistical Analysis

- Plasma FTC and IDV concentration-time data were analyzed by noncompartmental methods using WinNonlin Professional, version 3.0
- The following PK parameters were determined: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t½$, $AUC_{0-\infty}$, CL/F, and V_z/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, version 6.12
- The criteria for a lack of clinically significant difference between the test reference regimens were a 90% CI for the ratio of $AUC_{0-\infty}$ and C_{max} 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
Blood/Plasma
The methods for the determination of FTC and IDV in human plasma have been validated according to Triangle Pharmaceutical applicable standard operating procedures (SOP). FTC is extracted from human plasma by ——— IDV is extracted from human plasma by ———.

FTC-
Study samples were analyzed with up to 10 calibration standards and a minimum of 10 QC samples per analytical run. Correlation coefficients were all greater than 0.98. Inter-day precision, expressed as %CV, ranged from 6.17% to 9.55% for the human plasma assay. 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 ——ng/mL.

IDV-
Study samples were analyzed with up to 10 calibration standards and a minimum of 10 QC samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 5.37% to 10.09% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from 0.5% to 7.1% for the human plasma assay. The LLOQ of IDV for the study samples was —ng/mL.

FTC-104 Study Results

FTC Results-

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

Table 1. Arithmetic Mean (%CV) Values for FTC PK Parameters when Administered Alone or in Combination with IDV (N=12)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	λ_z (h^{-1})	t½ (h)	CL/F (mL/min)	V_z/F (L)
FTC	Mean	2.27	1.31	9.98	0.088	8.01	349	237
	%CV	33	45	24	15	14	21	16
FTC + IDV	Mean	2.05	1.38	10.10	0.081	8.82	349	271
	%CV	21	27	23	17	18	26	41

Table 2. Statistical Analysis of FTC PK Parameters (N=12)

PK Parameter	Statistical Value	FTC (reference)	FTC + IDV (test)	Statistical Analysis	FTC +IDV / FTC
$AUC_{0-\infty}$ (µg•h/mL)	Geom. Mean	9.75	9.84	GLS Ratio	1.009
				90% CI	0.939, 1.086
C_{max} (µg/mL)	Geom. Mean	2.19	2.01	GLS Ratio	0.920
				90% CI	0.817, 1.036

Reviewer Comment: Both AUC and C_{max} 90% CI values were within the Applicant's proposed 70% to 143% range. However, both AUC and C_{max} 90% CI values fell within the 80-125% range and this indicates that IDV does not significantly alter the PK of FTC when both drugs are administered together. No drug-drug interaction occurs between these two drugs when administered concomitantly.

IDV Plasma Results-

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

Table 3. Arithmetic Mean (%CV) Values for IDV PK Parameters when IDV is Administered Alone or in Combination with FTC (N=12)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	λ_z (h^{-1})	t½ (h)	CL/F (mL/min)	V_z/F (L)
IDV	Mean	6.95	0.77	15.08	0.576	1.25	1044	110
	%CV	34	22	42	19	21	41	38
IDV + FTC	Mean	6.73	0.94	14.88	0.553	1.29	997	107
	%CV	32	51	32	16	17	36	27

Table 4. Statistical Analysis of IDV PK Parameters (N=12)

PK Parameter	Statistical Value	IDV (reference)	IDV + FTC (test)	Statistical Analysis	IDV +FTC / IDV
$AUC_{0-\infty}$ (µg•h/mL)	Geom. Mean	13.87	14.14	GLS Ratio	1.019
				90% CI	0.886, 1.173
C_{max} (µg/mL)	Geom. Mean	6.57	6.41	GLS Ratio	0.976
				90% CI	0.842, 1.131

Reviewer Comment: *Both IDV AUC and C_{max} 90% CI values were within the Applicant's proposed 70% to 143% range. However, both AUC and C_{max} 90% CI values fell within the 80-125% range and this indicates that FTC does not significantly alter the PK of IDV when both drugs are administered together. No drug-drug interaction occurs between these two drugs when administered concomitantly.*

Conclusion

- A single dose of IDV had no effect on the PK of FTC

A single dose of FTC had no effect on the PK of IDV

FTC and Famciclovir Interaction Study (FTC-108)

Study Rationale

FTC-106 (Mass Balance Study) showed that the majority (80%) of an oral dose of emtricitabine (FTC) is excreted unchanged in the urine via renal tubular secretion. Drugs that are eliminated predominantly via urinary excretion could interact with FTC. One such drug is famciclovir (FCV), which is a purine nucleoside antiviral agent used clinically to treat acute uncomplicated herpes zoster and recurrent genital herpes. FCV is an oral prodrug that is almost completely converted to the active moiety, penciclovir (PCV). PCV is primarily eliminated by renal tubular secretion and glomerular filtration; therefore, these two drugs combined could compete for renal tubular secretion, which could affect the pharmacokinetics (PK) of either drug. For these reasons, a study to investigate the potential for a drug-drug interaction between FTC and FCV was conducted (Study FTC-108).

Study Objectives

Primary-

- To determine the effect of FCV/PCV on the PK of FTC
- To determine the effect of FTV on the PK of FCV/PCV

Secondary-

- To evaluate the safety of single doses of FTC and FCV/PCV administered in combination

Study Design

This was a single-center, open-label, randomized, three-way crossover study that enrolled 12 healthy volunteers. The study subjects were required to have normal renal function (estimated $CL_{cr} \geq 100$ mL/min). A one-week washout period separated each treatment.

Study Subjects Demographics

Of the 12 healthy volunteers enrolled in the study, 9 (75%) were male and 3 (25%) were female. Eleven of the 12 were Caucasian and one subject was Black. The average age and weight of the subjects were 35 years (range, 19 to 47 years) and 79 kg (range, 69-90 kg), respectively. The 12 subjects had estimated CL_{cr} values ranging from [redacted] mL/min (mean, 118.9 mL/min).

Study Drugs/Doses/Lot Numbers/Expiration Date/Batch Size

- FTC: 100-mg capsule/Lot # TP-0006-99099/Expiration Date-November 2000/Theoretical Batch Size- —— capsules
- FCV (FAMVIR™): 500-mg tablet/Lot # NDC-007-4117-13/Manufactured by SmithKline Beecham Pharmaceuticals (at the time of study, Philadelphia, PA)

Treatment Regimens

- Treatment A: 2 x 100-mg FTC capsules
- Treatment B: 1 x 500-mg FCV tablet
- Treatment C: 2 x 100-mg FTC capsules + 1 x 500-mg FCV tablet

PK Sampling Scheme to Measure FTC & PCV Concentrations

Plasma-

Whole blood samples were collected following each dose for analysis of FTC and PCV plasma concentrations. Blood samples were collected at pre-dose and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours post-dose administration.

Urine-

During each period, all urine passed by the subjects was collected over the following intervals: just prior to dosing (single void), and 0-4, 4-8, 8-12, 12-24, and 24-48 hours post-dose administration.

PK Analysis/Statistical Analysis

- Plasma FTC and PCV concentration-time data were analyzed by noncompartmental methods using WinNonlin Professional, version 3.1
- The following PK parameters were determined: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t½$, $AUC_{0-\infty}$, CL/F, V_z/F , CL_R , and A_e (amount of FTC excreted in urine)
- 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, version 6.12
- The criteria for a lack of clinically significant difference between the test and reference regimens were a 90% CI for the ratio of $AUC_{0-\infty}$ and C_{max} 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
Blood/Plasma
The methods for the determination of FTC and PCV in human plasma have been validated according to Triangle Pharmaceutical applicable standard operating procedures (SOP). A [redacted] bioanalytical method was used to determine FTC and PCV concentrations in plasma. The compounds were [redacted]

FTC-
Study samples were analyzed with up to 21 calibration standards and a minimum of 20 control samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 8.00% to 17.56% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -1.0% to 4.0% for the human plasma assay. The lower limit of quantitation (LLOQ) of FTC for the study samples was [redacted] ng/mL.

PCV-
Study plasma samples were analyzed with up to 12 calibration standards and a minimum of 16 QC samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 8.51% to 14.06% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -7.5% to 6.5% for the human plasma assay. The LLOQ of PCV for the study samples was [redacted] ng/mL.

Urine
FTC
To analyze FTC concentrations in human urine, an [redacted] was used and compounds were [redacted] Study samples were analyzed with up to 16 calibration standards and a minimum of 16 control samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 5.55% to 9.86% for the human urine assay. Inter-day accuracy, expressed as %bias, ranged from 2.7% to 8.0% for the human urine assay. The LLOQ of PCV for the study samples was [redacted] µg/mL.

PCV
To analyze PCV in human urine, [redacted] was used under similar conditions as for plasma samples. Study samples were analyzed with up to 16 calibration standards and a minimum of 12 control samples per analytical run. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 8.13% to 13.06% for the human urine assay. Inter-day accuracy, expressed as %bias, ranged from -14.9% to 3.0% for the human urine assay. The LLOQ of PCV for the study samples was [redacted] µg/mL.

FTC-108 Study Results

FTC Plasma Results-

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

Table 1. Arithmetic Mean (%CV) Values for FTC PK Parameters when Administered Alone or in Combination with FCV (N=12)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	AUC_{0-t} (µg•h/mL)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)
FTC	Mean	2.351	1.17	11.08	11.30	11.00	298	285
	%CV	20	21	11	10	9	10	16
FTC + FCV	Mean	2.120	1.46	10.37	10.61	11.56	326	334
	%CV	21	27	19	18	17	22	42

Table 2. Statistical Analysis of FTC PK Parameters (N=12)

PK Parameter	Statistical Value	FTC (reference)	FTC + FCV (test)	Statistical Analysis	FTC +FCV / FTC
$AUC_{0-\infty}$ (µg•h/mL)	Geom. Mean	11.24	10.43	GLS Ratio	0.928
				90% CI	0.870, 0.990
C_{max} (µg/mL)	Geom. Mean	2.307	2.075	GLS Ratio	0.899
				90% CI	0.801, 1.009

Reviewer Comment: Both AUC and C_{max} 90% CI values were inside the 80-125% range. This indicates that FCV does not have a statistically significant effect on the PK of FTC. Therefore, it can be concluded no drug-drug interaction occurs between these two drugs when administered concomitantly and no dose adjustment is needed.

PCV Plasma Results-

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

Table 3. Arithmetic Mean (%CV) Values for PCV PK Parameters when FCV is Administered Alone or in Combination with FTC (N=12)

TX	Statistic	C_{max} (µg/mL)	t_{max} (h)	AUC_{0-t} (µg•h/mL)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$ (h)
FCV	Mean	2.989	1.05	9.46	9.59	2.39
	%CV	22	32	19	19	13
FCV + FTC	Mean	2.809	0.96	8.52	8.66	2.45
	%CV	27	60	16	15	15

Table 4. Statistical Analysis of PCV PK Parameters (N=12)

PK Parameter	Statistical Value	FCV (reference)	FCV + FTC (test)	Statistical Analysis	FCV +FTC / FCV
$AUC_{0-\infty}$ (µg•h/mL)	Geom. Mean	9.42	8.58	GLS Ratio	0.911
				90% CI	0.835, 0.994
C_{max} (µg/mL)	Geom. Mean	2.918	2.716	GLS Ratio	0.931
				90% CI	0.782, 1.108

Reviewer Comment: AUC 90% CI values falls within the 80-125% range; however, the FCV C_{max} falls outside this range. Even though both PK parameters 90% CI did not fall within the 80-125% range, it can be concluded that FTC does not have a clinically significant effect on the PK of FCV. Therefore, it can be concluded no dose adjustment is necessary when FTC and FCV are administered together.

FTC Urine Results

Table 5 summarizes the arithmetic mean and %CV values for urinary excretion data (amount of drug excreted in the urine (A_e), renal clearance (CL_R), and % of dose excreted) for FTC alone and FTC combined with FCV.

Table 5. Arithmetic Mean (%CV) Values for FTC Urinary Excretion Data when Administered Alone or in Combination with FCV (N=12)

TX	Statistic	A_e (mg)	% of Dose Excreted	CL_R (mL/min)
FTC	Mean	94.40	47	145.69
	%CV	25	25	32
FTC + FCV	Mean	118.81	59	201.48
	%CV	35	35	47

Reviewer Comment: The mean urinary excretion data observed after FTC was administered alone were substantially less than seen in other FTC studies conducted earlier. The urinary excretion results for FTC when combined with FCV were in agreement with previous FTC urinary excretion data. This observation may indicate some type of collection error during the FTC alone treatment period.

PCV Urine Results

Table 6 summarizes the arithmetic mean and %CV values for urinary excretion data (A_e, CL_R, and % of dose excreted) for FTC alone and FTC combined with FCV.

Table 6. Arithmetic Mean (%CV) Values for PCV Urinary Excretion Data when FCV is Administered Alone or in Combination with FTC (N=12)

TX	Statistic	A_e (mg)	CL_R (mL/min)
FCV	Mean	211.75	377.67
	%CV	17	20
FCV + FTC	Mean	184.79	360.14
	%CV	9	14

Conclusion

- A single dose of FCV co-administered with FTC had no clinically significant effect on the single-dose PK of FTC
- A single dose of FTC co-administered with FCV had no clinically significant effect on the PK of PCV

Emtricitabine and Tenofovir 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 —— 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_τ 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_τ, λ_z, $t_{1/2}$, 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 AUCτ, $C_{max,ss}$ 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 Triangle Pharmaceutical applicable standard operating procedures (SOP). A [redacted] bioanalytical 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 -9.8% to 3.8%. For TDF, inter-day precision, expressed as %CV, ranged from 5.17% to 14.43% and inter-day accuracy, expressed as %bias, ranged from -9.0% to 2.4% for the human plasma assay. The lower limit of quantitation (LLOQ) of FTC for the study samples was [redacted] g/mL and LLOQ for TDF was [redacted] g/mL.

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)	$t_{1/2}$ (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 90% CI	1.000 0.922, 1.086
$C_{max,ss}$ (µg/mL)	Geom. Mean	273	281	GLS Ratio 90% CI	1.026 0.951, 1.106
$C_{min,ss}$ (µg/mL)	Geom. Mean	52	53	GLS Ratio 90% CI	1.020 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

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6.1.5 Special Population Study and Pharmacometric Consult for Renal Impairment Study

Renal Impairment Study (FTC-107)

Study Duration

05Nov1999 through 19April2000

Investigators and Study Center

Study Rationale

Early pre-clinical studies demonstrated that emtricitabine (FTC) is primarily eliminated by renal excretion, with > 50% of an oral dose excreted as unchanged FTC in the urine of mice and monkeys. At the time the present study was designed, the Mass Balance Study FTC-106 was being conducted to determine the extent of renal excretion of FTC following an oral dose. Since then, FTC-106 results have shown renal excretion (glomerular filtration along with tubular secretion) is the primary elimination route of FTC in plasma. Additionally, approximately 65-70% of an oral FTC dose is excreted in urine as unchanged parent drug in humans, which confirms FTC is primarily eliminated as unchanged drug via urinary excretion. Therefore, renal impairment is likely to significantly alter the pharmacokinetics (PK) of FTC, which in turn may necessitate dosage adjustment among patients with renal impairment. FTC-107 was designed to determine the effect of renal impairment on the PK of FTC following a single oral dose in subjects with varying degrees of renal impairment.

Study Objectives

Primary-

- To determine the effect of renal impairment on the pharmacokinetics of FTC following a single oral dose in subjects with varying degrees of renal insufficiency in comparison to subjects with normal renal function

Secondary-

- To determine the safety of a single oral dose of 200-mg FTC in subjects with varying degrees of renal insufficiency
- To determine the effect of hemodialysis on the elimination of FTC in subjects with end-stage renal disease (ESRD)

Study Design and Dosing Procedures

An open-label, parallel-group study which planned to enroll 6 subjects in each of the following five groups, with varying degrees of renal function as determined by estimated creatinine clearance (CL_{cr}):

Group	Description	Estimated CL_{cr} (mL/min)
I	Normal renal function	>80 mL/min
II	Mild renal impairment	50-80 mL/min
III	Moderate renal impairment	30-49 mL/min
IV	Severe renal impairment	< 30 mL/min
V	ESRD (requiring hemodialysis)	functional anephric

Estimated CL_{cr} at study entry was determined using the Cockcroft Gault method based on serum creatinine (average value) at screening and baseline (Day 0). For subjects in Groups I-IV, an in-house, 24-hour urine collection was performed on Day 0 of Dose Period I for confirmatory determination of CL_{cr}.

All subjects (Groups I through V) participated in Dose Period I (Day 0 through Day 3 for subjects in Groups I and II; Day 0 through Day 4 for subjects in Groups III through V). On Day 1 of Dose Period 1, a single oral dose of 200-mg FTC was administered to each subject, following an overnight fast. Serial blood and cumulative urine samples were collected up to 48 hours (Groups I and II) and up to 72 hours (Groups III and IV) following drug administration. During this period for Group V subjects, the FTC dose

was administered on an off-dialysis day (shortly after completion of a 3 hour hemodialysis) and blood samples were collected up to 72 hours following dosing.

After a minimum 1-week washout period, Group V received a second single FTC oral 200-mg dose. Dialysis started 1.5 hours after dose administration and continued for 3-hours post-dose administration.

Study Subjects

In all, 29 subjects enrolled and 28 subjects were evaluable. There were five study groups. These groups were stratified based on calculated creatinine clearance using the Cockcroft Gault method, and followed the scheme outlined in the *Guidance for Industry* that addresses renal impairment studies. Each group had 5-6 subjects. Demographic characteristics of the subjects who participated in the trial are summarized below in Table 1.

Table 1. Demographic Summary by Group for FTC-107 Study Subjects

Demographics	Group I (n=6)	Group II (n=6)	Group III (n=6)	Group IV (n=5)	Group V (n=6)
Gender (n, %)					
Female	1 (17)	5 (83)	1 (17)	0	1 (17)
Male	5 (83)	1 (17)	5 (83)	5 (100)	5 (83)
Ethnic Origin (n, %)					
African	3 (50)	3 (50)	4 (67)	3 (60)	6 (100)
Caucasian	3 (50)	3 (50)	2 (33)	2 (40)	0
Age (Years)					
Median	60.5	75.0	66.5	61.0	39.0
Min, Max	47.0, 74.0	69.0, 79.0	54.0, 78.0	48.0, 78.0	31.0, 54.0
Weight (kg)					
Median	79.0	74.7	66.5	76.5	76.2
Min, Max	68.0, 84.5	62.5, 93.0	56.0, 103.5	72.9, 113.0	66.0, 93.0
Avg. Estimated CL_{cr} (mL/min)					
Median	100.3	62.0	42.1	24.4	8.8
Min, Max					

In this study, enrollment was open to subjects between the ages of 18 and 80; however, the majority of the subjects were above 60 years of age.

Reviewer Comment: The study subjects enrolled into FTC-107 were much older than the anticipated age group that will typically take FTC once approved. Since the 'Renal Impairment Guidance for Industry' recommends to use study subjects that will mirror your target population, this was clearly a deviation from the Guidance recommendation. The Applicant does make a comment about this issue and provides a comparison with younger HIV-infected subjects from Study FTC-303 as a comparison of plasma FTC $AUC_{0-\infty}$ versus estimated CL_{cr}. This comparison looks at younger HIV-infected subjects with normal renal function and compares them to the FTC-107 control group (median age 60.5), but lacks any comparisons for the other groups with renal impairment. The HIV-infected younger population group AUC values were similar to the older control group in Study FTC-107.

Formulation, Dose, and Batch Number

The test product was emtricitabine administered as two 100-mg gelatin capsules (Lot Number TP-0006-99044).

Blood Sampling

Blood samples were collected at the following time points:

- Groups I and II: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose
- Groups III and IV: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose
- Group V: Dose Period 1 (off dialysis): same as Group III and IV above
  Dose Period 2 (on dialysis): pre-dose and at 0.5, 1, and 1.5 hours post-dose and then at 0.5, 1, 1.5, 2, 2.5, and 3 hours after the start of dialysis and immediately prior to the end of dialysis (if $\geq$ 5 minutes later than 3 hours after the start of dialysis)

Both arterial and venous blood samples were collected for Dose Period 2.

Urine Samples

Dose Period 1:

Group I and II were collected over the intervals of 0-12, 12-24 and 24-48 hours post-dose.

Group III and IV were collected over the intervals of 0-12, 12-24, 24-48, and 48-72 hours post-dose.

Dialysate Samples

Total cumulative dialysate samples were collected from subjects in Group V prior to the initiation of dialysis and at hourly intervals during the dialysis period.

Assay/Analytical Method

A validated bioanalytical method was used to determine FTC concentrations in plasma, urine, and dialysate. Triangle Pharmaceuticals, Inc., Durham, NC, validated the method. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 6.3 to 7.3% for the human plasma and dialysate assay and 5.5 to 10.1% for the human urine assay. Inter-day accuracy, expressed as %bias, ranged from 1.0 to 9.4% for the human plasma and dialysate assay and -2.4 to 6.8% for the human urine assay.

Pharmacokinetic Analysis

Standard PK measures were calculated using a non-compartmental approach (WinNonlin™).

Pharmacokinetic Results

Dose Period 1

The key pharmacokinetic parameter estimates for FTC for all 5 groups following a single oral 200-mg dose are summarized below in Table 2.

Table 2.

Study Group (CL_{cr})	Statistics	C_{max} (µg/mL)	t_{max} (hr)	AUC_{0-t} (µg·h/mL)	$AUC_{0-\infty}$ (µg·h/mL)	t½ (hr)	CL/F (mL/min)
I (n=6) > 80 mL/min	Mean	2.20	1.84	11.38	11.78	14.19	302
	%CV	29	51	26	25	24	31
II (n=6) 50-80 mL/min	Mean	3.78	1.75	19.39	19.86	11.50	168
	%CV	23	43	6	6	9	6
III (n=6) 30-49 mL/min	Mean	3.18	1.67	24.44	25.08	15.51	138
	%CV	17	45	22	23	7	21
IV (n=5) < 30 mL/min	Mean	2.84	2.10	32.32	33.73	16.40	99
	%CV	24	64	6	6	5	6
V (n=5) Functional anephric Requiring hemodialysis	Mean	2.83	2.80	46.81	53.22	23.00	64
	%CV	17	45	18	19	8	19

- AUC values were significantly greater in subjects with renal impairment, ranging from ~ 2 to 4.5 fold higher in subjects with mild to severe impairment than those in the control group (Group 1)
- C_{max} values increased in subjects with renal impairment, but to a much lesser extent, ranging from 1.3 to 1.8 fold higher and the extent of increase was independent to the degree of renal function

The summary results for the statistical analysis of key FTC PK parameters by Group are listed below in Table 3.

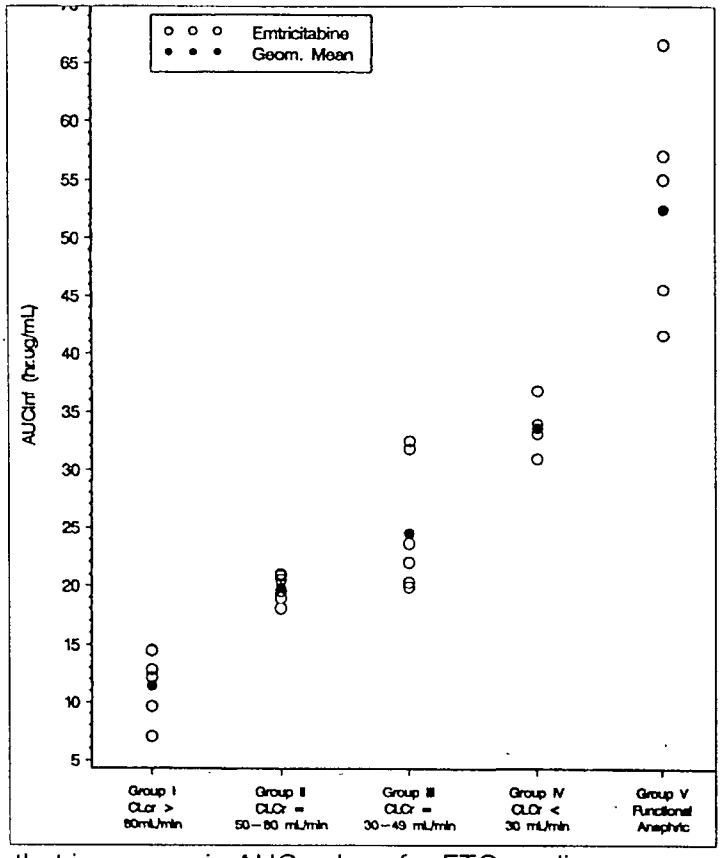
Table 3. Statistical Analysis of Key FTC PK Parameters by Group

PK Parameter	Statistic	Group II vs. Group I	Group III vs. Group I	Group IV vs. Group I	Group V vs. Group I
$AUC_{0-\infty}$ (hr·µg/mL)	*GLSM Ratio 90% CI	1.73 1.44, 2.09	2.15 1.79, 2.59	2.95 2.43, 3.58	4.59 3.78, 5.57
C_{max} (µg/mL)	*GLSM Ratio 90% CI	1.76 1.36, 2.27	1.49 1.16, 1.93	1.32 1.01, 1.73	1.33 1.02, 1.74
t_{max} (hr)	*GLSM Ratio 90% CI	0.95 0.41, 1.50	0.91 0.36, 1.45	1.14 0.57, 1.72	1.52 0.92, 2.10
t½ (hr)	*GLSM Ratio 90% CI	0.83 0.73, 0.94	1.12 0.98, 1.27	1.18 1.03, 1.35	1.66 1.44, 1.90
CL/F (mL/min)	*GLSM Ratio 90% CI	0.58 0.48, 0.69	0.47 0.39, 0.56	0.34 0.28, 0.41	0.22 0.18, 0.26

*GLSM Ratio denotes Geometric Least Square Mean Ratio

Plots of FTC PK parameter estimates in individual subjects across Groups are presented below in Figure 1.

Figure 1. Plots of FTC PK Parameter Estimates across Groups (Dose Period 1)



- It appears that increases in AUC values for FTC are linear as renal function (CL_{cr}) decreases.

FTC Urine Results

The cumulative urinary recovery and CL_R values of FTC by Group are summarized below in Table 4.

Table 4. Cumulative Urinary Recovery and CL_R Values of FTC, Mean (Range), by Group

Parameter	Group 1 (n=6)	Group II (n=6)	Group III (n=6)	Group IV (n=5)
% Dose Excreted as FTC	70.88	69.74	46.57	29.09
CL_R (mL/min)	213.3	121.4	68.6	29.5
CL_R:CL/F	0.73	0.72	0.48	0.30
CL_{cr} (mL/min)	101.9	56.7	41.9	22.0

- For subjects in Groups I and II, approximately 70% of the orally administered FTC dose was recovered as the unchanged parent drug, which is consistent with findings in previous studies (FTC-101 conducted in HIV-infected subjects and FTC-106 Mass Balance study conducted in healthy subjects)
- The mean CL_R values for subjects in Groups II, III, and IV were 57%, 32%, and 13% of the values in subjects in Group I, respectively
- Subjects 103 and 104 in Group 1 have unusual amounts of FTC excreted in urine compared to other subjects in their Group(103, 221.4 mg excreted and 104, 69.5 mg excreted)

Linear Regression Analysis of CL/F and CL_R vs. CL_{cr}

- There is a statistically significant linear relationship between CL/F and CL_{cr} as described by the equation of CL/F = 31.58 + (2.64 * CL_{cr}) with a $r^2 = 0.94$
- There is a linear relationship (to a lesser degree) between CL_R and CL_{cr} as described by the equation CL_R = -7.7 + (2.09 * CL_{cr}) with a $r^2 = 0.61$

Reviewer Comment: As mentioned previously, subjects 103 and 104 from Group I are extreme outliers with respect to amount of FTC excreted in urine and % FTC excreted in urine. The linear relationship for CL_R vs. CL_{cr} would be much stronger if these outliers were omitted.

Dose Period 2

Individual estimates and summary statistics of FTC PK parameters in Group V on hemodialysis are listed below in Table 5.

Prior to Hemodialysis N = 6	Mean (%CV) Venous Plasma	
C_{max}, (μg/mL)	2.28 (41)	
t_{max}, (hr)	1.24 (21)	
AUC_{0-t}, (h·μg/mL)	1.56 (35)	
During Hemodialysis N = 6	**Mean (%CV) Atrial Plasma**	**Mean (%CV) Venous Plasma**
C_{max}, (μg/mL)	2.63 (26)	2.31 (29)
t_{max}, (hr)	0.17 (155)	0.58 (206)
C_{last}, (μg/mL)	1.13 (25)	1.06 (43)
AUC_{0-t}, (h·μg/mL)	5.87 (5)	5.12 (25)
Lambda Z (hr^{-1})	0.223 (19)	0.193 (24)
t½ (hr)	3.21 (21)	3.79 (26)

- FTC concentrations were measurable in all dialysate samples collected over the entire 3-hour hemodialysis period.
- An average of 54.8 mg of FTC was recovered in the dialysate over a 3-hour dialysis period, representing 27.4% of the FTC dose administered
- The hemodialysis CL of FTC, calculated based on dialysate recovery, averaged 78.1 mL/min
- The mean dialysate CL (CL_D) value of 78.1 mL/min is slightly greater than the CL/F of FTC without hemodialysis (64 mL/min) in Group V subjects
- Additionally, this CL_D value is slightly greater than the mean CL_R (69 mL/min) of FTC in Group III with moderate impairment
- Mean extraction ratio (ER) is ~ 40%

FTC's combined high water solubility, low molecular weight (247), and negligible plasma protein binding (~ 4%) plays a role in FTC being efficiently extracted from plasma via hemodialysis. Although FTC was efficiently removed by hemodialysis, the plasma FTC concentrations were not significantly lower during and post hemodialysis as compared to those observed pre-dialysis or those on the off-dialysis day (Dose Period 1). This is most likely due to the fact that FTC has a relatively large volume of distribution (Vd) (Vd = 385 L in Group I and 127 L in Group V) and redistribution of FTC from the peripheral compartment into the central compartment could occur following removal of FTC via hemodialysis. Therefore, hemodialysis as performed in Study FTC-107 (400-mL/min dialysate flow rate, 3 times a week for 3 hour duration) is not expected to have a clinically significant effect on plasma FTC exposures. Patients who undergo prolonged or continuous hemodialysis would have a greater effect on removal of FTC and systemic exposure. Since continuous or prolonged dialysis was not studied, no recommendation can be given.

FTC Dosing Recommendations for Patients with Renal Impairment
Table 6 below contains the Applicant's proposed renal impairment dosing recommendations.

Table 6. FTC Dosing Recommendations for Patients with Renal Impairment

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

Reviewer Comment: The Applicant was asked to provide predicted AUC, C_{max}, and concentration vs. time profiles for the proposed renal dosage adjustment and these data have been submitted. Please see Applicant's Response section for these values.

Safety Results
No deaths or other serious adverse events (SAEs) were reported in this study. None of the subjects discontinued as a result of an adverse event (AE).

The Applicant provided the following response to requests made during the NDA review.
Applicant's Response

Please provide your rationale for selecting 50 mL/min as your cutoff point for emtricitabine dose reduction from 200-mg daily to 100-mg daily.

Applicant's Response: No dose related adverse events were identified in study FTCB-101 in which patients were dosed with FTC 300-mg QD for 8-weeks. Considering that the PK of FTC are dose-proportional, this represents approximately 1.5-fold the exposure (AUC) of the 200-mg dose and would be similar to the drug levels expected in subjects with a CL_{cr} of 50 to 80 mL/min.

To further assess the safety of long-term FTC administration to patients with mild renal impairment, selected safety parameters were tabulated for 40 patients who had a baseline CL_{cr} of 50 to 80 mL/min and compared to patients with normal renal function. The data were tabulated based on the Integrated Summary of Safety and NDA Safety Update. No clinically significant difference was observed after a median time on study

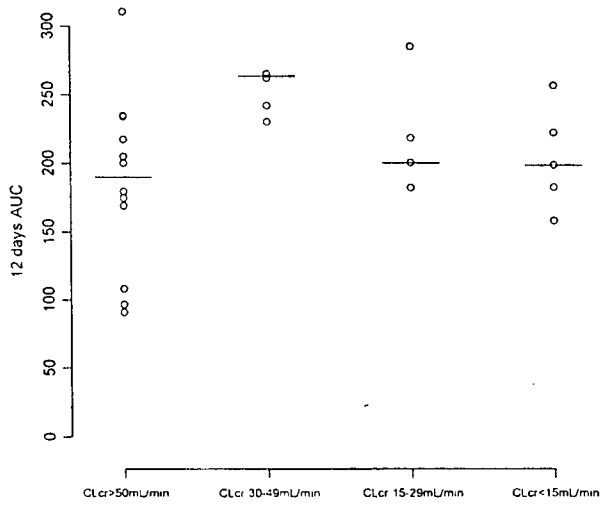
drug of over 48 weeks. In addition, there were no serious adverse events (SAEs) or Grade 3/4 clinical adverse events or laboratory toxicities reported in 6 other patients with moderate to severe renal dysfunction at baseline (CL_{cr} range 29-49.9 mL/min) with a median time on study drug of 48.1 weeks.

Pharmacometric (PM) Consult

To determine predicted exposure (AUC, C_{max}, and concentration versus time profile) at the proposed dosing regimens, a Pharmacometric consult was requested

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. Dr. Zheng's analysis results are listed in Figure 2, 3, and 4.

Figure 2. 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 3 and 4.

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

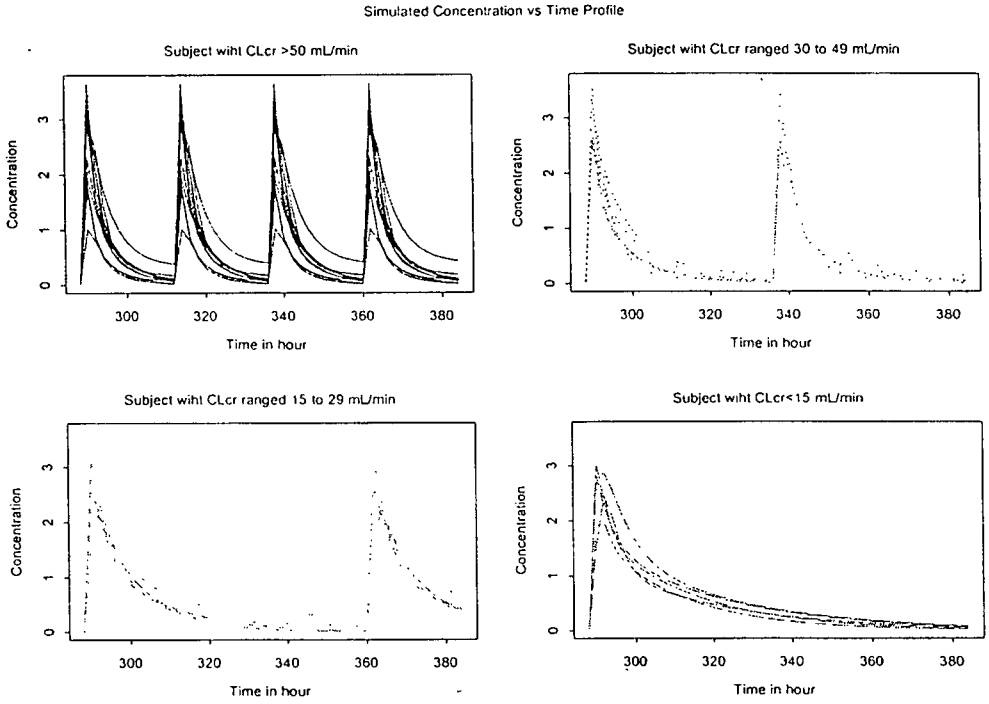


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Figure 4. Simulated FTC $C_{\tau,ss}$ Values for Varying Degrees of Renal Impairment

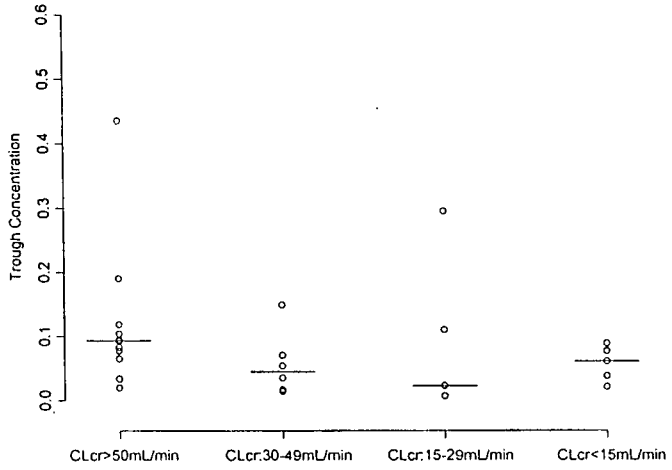


Figure 3 shows the simulated steady-state maximal concentration ($C_{max,ss}$) in subjects with CLcr < 29 mL/min are somewhat lower than the $C_{max,ss}$ in the subjects with CLcr $\geq$ 30 mL/min.

Figure 4 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} 30-49 mL/min, CL_{cr} 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 typically 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. Therefore, the proposed dosing recommendations for the administration of FTC in patients with renal impairment are acceptable.

Conclusions

- Urinary excretion is the primary route of FTC elimination, with ~ 70% of an oral dose recovered in the urine as unchanged drug in subjects with normal renal function and mild renal impairment
- The PK of FTC was significantly affected by renal impairment. There was a graded increase in AUC values (by ~ 2 to 4.5 fold) and corresponding graded decreases in CL/F values as the degree of renal impairment increased.
- C_{max} values increased by 1.3 to 1.8 fold in subjects with mild to severe renal impairment
- There was a statistically significant linear relationship between CL/F value of FTC and CL_{cr} value. Thus, individual CL/F values of FTC can be estimated based on CL_{cr} values
- Based on the extent of altered PK, FTC should be dose adjusted for mild to severe renal impairment (CL_{cr} values < 80 mL/min)
- FTC is dialyzable and efficiently extracted from plasma by hemodialyzer in subjects with ESRD.
- Hemodialysis procedures as performed in this study (~ 3 hours of duration, three times a week at a dialysate flow rate of ~ 400 mL/min) is not expected to have a clinically significant effect on plasma FTC exposures
- 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.
- The proposed dosing recommendations for the administration of FTC in patients with renal impairment are acceptable.

Pharmacometric Consult for Renal Impairment Study
Jenny J. Zheng, Ph.D. Review

The sponsor conducted a pharmacokinetic study in renal impaired subjects (Study 107). Please refer to Dr. DiGiacinto's review for the detailed findings from the study. Based on the study the sponsor proposed dose adjustments in renal impaired subjects as shown in the following table:

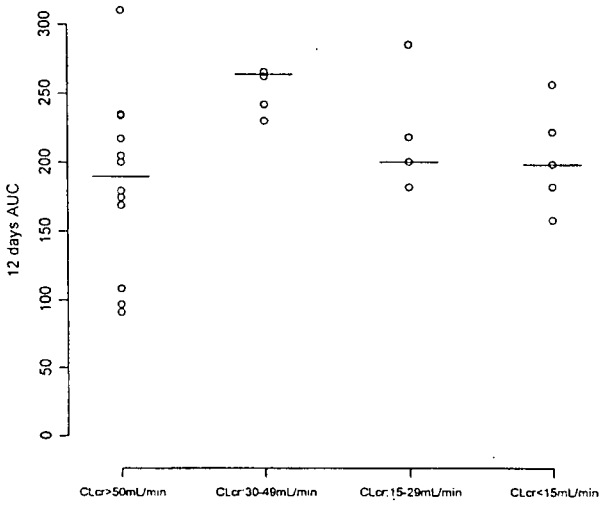
Creatinine Clearance	200 mg emtricitabine
>= 50mL/min	Q24h
30-49 mL/min	Q48h
15-29 m/min	Q72h
<15mL/min including patients requiring hemo-dialysis	Q96h

Two parameters, cumulative AUC over 12 days and the trough concentration at steady state, are compared between groups based on proposed dose regimens. Cumulative AUC over 12 days is referred to as 12-day AUC.

Assuming emtricitabline has linear pharmacokinetics, the pharmacokinetics of the drug at steady state were simulated using the single dose data. It was found that the 2-compartment model with first-order delayed absorption and first-order elimination best describes the data. The estimated pharmacokinetic parameters were then used to simulate the concentration time profiles at steady state and the proposed dose regimens.

The 12-day AUC values were calculated by multiplying simulated steady state $AUC_{0-\tau}$ by the number of doses the subjects would receive in 12 days. The number of doses are 12, 6, 4, and 3 for subjects with creatinine clearance (CLcr) >50mL/min, 30-49 mL/min, 15-29 mL/min, and <15mL/min, respectively. The 12-day AUC values for each subject and each group according to the CLcr are shown in Figure 1. The circles represent the individual data and the line is the median value in the group.

Figure 1. Simulated AUC in 12 days



The results showed that 12-day AUC values were similar among all groups except in subjects with CLcr between 50 and 80 mL/min. Subjects with CLcr between 50-80 mL/min has higher 12-day AUC values than other subjects.

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

Figure 2.

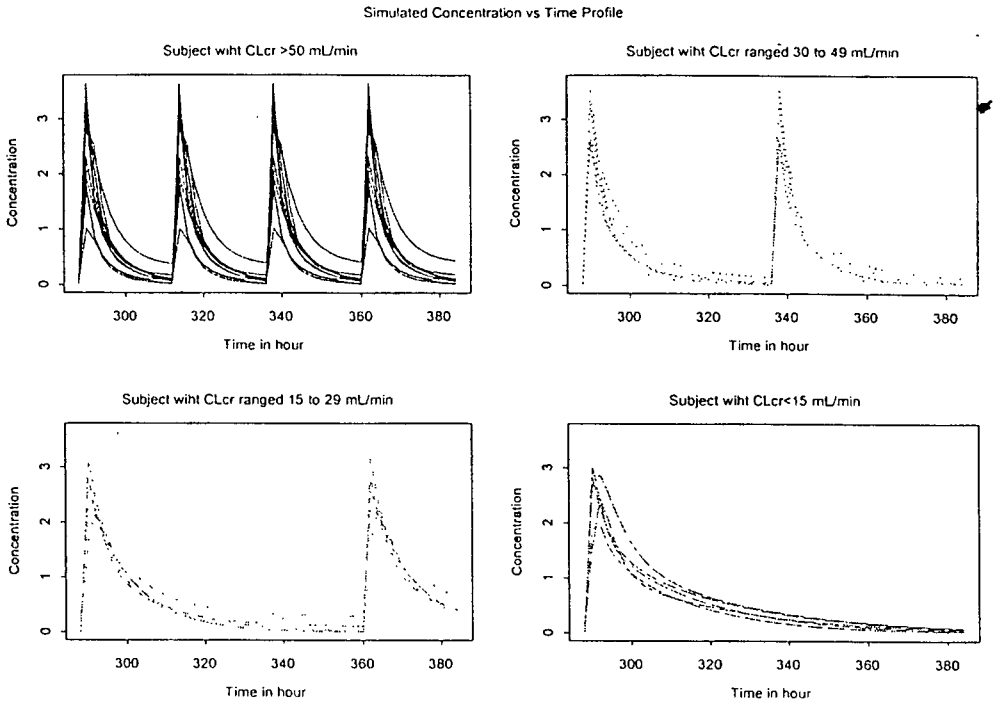

Figure 2 shows that the steady state maximal concentration (Cmax,ss) in subjects with CLcr< 29 mL/min are somewhat lower than the Cmax,ss in the subjects with CLcr>=30 mL/min.

Figure 3.

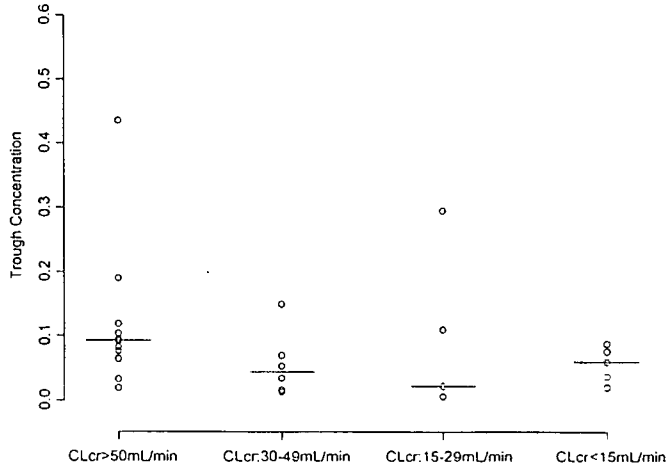

Figure 3 shows the steady-state trough concentrations ($C_{trough,ss}$) in each dosing group.

The median $C_{trough,ss}$ are 0.0933, 0.04455, 0.0225, and 0.0604 µg/mL in the subjects with CLcr >50mL/min, CLcr from 30 to 49 mL/min, CLcr from 15 to 29 mL/min, and CLcr <15mL/min, respectively. The $C_{trough,ss}$ in subjects with CLcr >80 mL/min is 0.0836 µg/mL. The results show that $C_{trough,ss}$ in subjects with CLcr < 49 mL/min are lower as compared with $C_{trough,ss}$ in subjects who take the drug q24h, especially for the subjects with CLcr ranged from 15-29 mL/min, in which $C_{trough,ss}$ is about 0.0225 µg/mL. To justify the proposed dose regimens, $C_{trough,ss}$ was compared with *in vitro* 50% inhibitory concentration (IC_{50}) and 90% inhibitory concentration (IC_{90}) of FTC. The IC_{50} and IC_{90} are 0.008 and 0.055 µM (or 0.002 and 0.014 µg/mL), respectively.

The $C_{trough,ss}$ was also calculated using observed concentrations and the accumulation factor. Assuming a linear pharmacokinetic of the drug, accumulation factor was calculated according the proposed dose regimens. The $C_{trough,ss}$ was calculated by multiplying the accumulation factor with the C_{24}, C_{48}, and C_{72} concentrations after the single dose, depending on what dosing group the subjects belong to. For example, for subjects who receive the drug every day, C_{24} was used and for the subjects who receive the drug every 48 hours, C_{48} was used. The last sample was collected at 72 hour. Therefore, C_{96} was not available for the subjects who should receive the drug every 96 hours. C_{96} was calculated based on C_{72} and the half life in the subject and an assumption of log-linear decay.

The calculated mean accumulation factors are 1.5, 1.3, 1.1, 1.1, and 1.1 for subjects with CLcr>80mL/min, CLcr from 50 to79 mL/min, CLcr from 30-49 mL/min, CLcr from 15-29 mL/min, and CLcr<15 mL/min, respectively. The predicted mean $C_{trough,ss}$ are 0.0539, 0.0928, 0.0568, 0.0594, and 0.0926 □g/mL, for subjects with CLcr > 80 mL/min, CLcr ranged from 50 to79 mL/min, CLcr ranged from 30-49 mL/min, CLcr ranged from 15- 29 mL/min, and CLcr<15 mL/min, respectively.

The sponsor modeled the data from renal impairment study and conducted a simulation to support the dose adjustment in renal impaired subjects. A two-stage approach was used in sponsor's analysis. The individual concentration time profile was first fitted using WinNonlin. A two-compartment model with delayed and first order absorption and first order elimination was used. The estimated parameters including total clearance (CL/F), inter-compartment clearance (CLD2/F), volume of central compartment (V1/F), volume of peripheral compartment (V2/F) absorption rate constant (k01), and lag time (LT) were used to test their correlation with creatinine clearance (CLcr) by linear regression analysis. Weighted linear regression analysis revealed strong correlations with both the systemic clearance (CL/F) and the distribution clearance (CLD2/F). While there were also correlations between CLcr and K01 and V2/F, these relationships were not striking and may simply be a reflection of the covariance of these parameters with CL/F and CLD2/F.

The simulations were conducted using the model. One hundreds profiles were generated within each group. CL/F and CLD2/F were expressed as linear functions of CLcr with all other parameters and their variances being estimated by their overall least-squares means and standard errors from weighted ANOVA. Individual estimates of CLcr for subjects were sampled from a uniform distribution within the assigned ranges for the four groups. Log-linear regression with log-normal inter-individual error terms were necessary to constrain the clearance terms to be greater than zero. A covariance term

was used for CL/F and CLD2/F. The off-diagonal element of the correlation matrix was estimated by averaging the elements of the correlation matrix for the parameter.

Pharmacokinetic parameters that were independent of renal function, K01, V1, V2 and LT, were sampled from multivariate log-normal distributions for each simulated subject. Off-diagonal elements of the correlation matrix for these parameters were estimated by averaging the corresponding elements of the correlation matrices from pharmacokinetic model fits across all subjects in FTC-107. The simulated results are shown in the following table. The predicted median Cmin values are 0.04, 0.07, 0.049, and 0.035 µg/mL for CLcr>50mL/min, 30-49 mL/min, 15-29mL/min, and <15mL/min, respectively.

Creatinine Clearance Range mL/min	200 mg emtricitabine administered every		C_{max} µg/mL)	C_{min} (µg/mL)	Average (µg/mL)
> 50 mL/min	24 hours	min			
		median	2.08	0.040	10.7
		max			
30-49 mL/min	48 hours	min			
		median	3.28	0.070	14.0
		max			
15-29 mL/min	72 hours	min			
		median	3.26	0.049	11.7
		max			
< 15 mL/min	96 hours	min			
		median	3.43	0.035	9.9
		max			

The sponsor's analysis was questionable. The deficiencies are the followings:

1. The estimated geometric mean of absorption rate constant are 2.65, 2.56, 7.10, and 1.57 h^{-1} in the subjects with CLcr >50 mL/min, 30-49 mL/min, 15-29 mL/min, and <15 mL/min, respectively. However, in the simulation a mean of 0.5851 h^{-1} was used.
2. The effect of renal function represented as CLcr was modeled on both total clearance (CL/F) and the distribution clearance (CLD2/F). The physiological rationale of CLcr impacting CLD2/F is lacking.
3. The way of calculating the off-diagonal elements of the correlation matrix is not acceptable. In the analysis, the off-diagonal elements of the correlation matrix for these parameters were estimated by averaging the corresponding elements of the correlation matrices from pharmacokinetic model fits across all subjects in FTC-107. However, the correlation matrix for each individual fit reflects the correlation between the parameters in the individual. The averaging the values across individual does not reflect the correlation of the parameters between subjects.

RECOMMENDATION:

Based on the reviewer's analysis, it appears that the proposed dose reduction in renal impaired subjects is reasonable considering both 12-day AUC values and the simulated steady-state trough concentrations.

6.1.6 Supportive Studies

Lamivudine Encapsulation Study (FTC-112)

Study Objectives

- To compare the bioavailability (BA) of EPIVIR™ (from the United States and South Africa) versus the encapsulated South African EPIVIR™ tablets from the same lot obtained from a commercial source
- To compare the bioequivalence (BE) of EPIVIR™ tablets obtained from a commercial source in South Africa to tablets obtained from a commercial source in the United States

Study Design

This was an open-label, randomized; balanced three-way crossover study to evaluate the single-dose pharmacokinetics (PK) of lamivudine (3TC) administered as three dosage forms. Twenty-six healthy volunteers were enrolled and 24 subjects completed all three treatments. A one-week washout interval separated each treatment. All treatments were administered under fasting conditions.

Study Subjects Demographics

Fourteen male (54%) and 12 (46%) female subjects enrolled into FTC-112. The majority of subjects were Caucasian (23/26, 88%) with 1 Asian, 1 American Indian, and 1 Hispanic, respectively. The mean age and weight of study subjects were 36 years (range, 22 to 51) and 73.2 kg (range, 61 to 90 kg).

3TC Formulations/Lot Number/Expiration Date/Batch Size (when available)

- Treatment A: 1 x 150-mg EPIVIR™ tablet (United States [US]source)/Lot # PZPO827/October, 2000
- Treatment B: 1 x 150-mg EPIVIR™ tablet (South African [SA] source)/Lot # W1088HCA/July, 2000
- Treatment C: 1 x 150-mg encapsulated SA EPIVIR™ tablet/Lot # TP-0010-96-G/July, 2000/[redacted] capsules

PK Sampling Scheme

Blood samples for measurement of 3TC plasma concentrations were collected pre-dose (time 0) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after each dose of 3TC.

PK Analysis

- Plasma 3TC concentration-time data were analyzed by noncompartmental methods using WinNonlin, Professional, version 3.0
- The following PK parameters were calculated: C_{max}, t_{max}, AUC_{0-t}, $t½$, $AUC_{0-\infty}$, and CL/F
- All PK parameters except for t_{max} were log transformed before statistical analyses. SAS, version 6.12 was used to compare Treatment B (SA tablet) vs. Treatment A (US tablet), Treatment C (SA encapsulated) vs. Treatment B (SA tablet), and Treatment C (encapsulated SA) vs. Treatment A (US tablet)
- 90% CI were calculated for each parameter and the geometric least-squares mean (GLS) ratios were used and reported as the primary estimates of relative BA

3TC Assay/Analytical Method

A validated [redacted] bioanalytical method was used to determine 3TC concentrations in plasma.

Study plasma samples were analyzed with up to nine calibration standards and three levels of QC samples per analytical run. Correlation coefficients were all greater than 0.9992. Inter-day precision, expressed as %CV, ranged from 2.41% to 3.54% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -2.22% to -0.10% for the human plasma assay. The lower limit of quantitation (LLOQ) for 3TC was [redacted] ng/mL.

FTC-112 Study Results

Table 1 provides the 3TC arithmetic mean (%CV) PK parameter estimates by treatment and Table 2 provides the 3TC BE statistical results of treatment comparisons.

Table 1. Descriptive Statistics for 3TC PK Parameters by Treatment

Treatment	Statistic	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg•h/mL)	$t_{1/2}$ (h)	CL/F (mL/min)
EPIVIR™ US (N=26)	Mean	1.70	0.88	7.00	6.32	364
	%CV	23	35	14	7	14
EPIVIR™ SA (N=25)	Mean	1.79	0.86	7.07	6.35	362
	%CV	23	36	15	14	16
Encapsulated EPIVIR™ SA (N=25)	Mean	1.91	0.94	7.02	6.37	363
	%CV	22	27	14	10	14

Table 2. 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	1.01	0.99	1.00
90% CI	0.98, 1.05	0.95, 1.03	0.97, 1.04
C_{max} (µg/mL)			
GLS Mean Ratio	1.06	1.05	1.11
90% CI	0.98, 1.14	0.97, 1.13	1.03, 1.20

Reviewer Comment: 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.

Conclusion

- The encapsulated 150-mg SA EPIVIR™ tablet formulation is BE to 150-mg EPIVIR™ tablets from both the US and SA sources. The encapsulated SA tablet formulation was used in clinical study FTC-302.
- The 150-mg EPIVIR tablet manufactured in SA is BE to the 150-mg EPIVIR™ tablet manufactured in the US (reference treatment)

Stavudine Over-Encapsulation Study (FTC-113)

Study Objectives

- To compare the bioavailability (BA) of 40-mg Zerit™ (d4T) capsules versus the over-encapsulated 40-mg d4T capsules from the same Lot obtained from a commercial source

Study Design

This was a single-center, open-label, randomized, two-way crossover study. Eighteen healthy volunteers were enrolled and completed FTC-113. A one-week washout period separated each single-dose treatment and treatments were administered in a fasted state.

Study Subjects Demographics

Of the 18 enrolled subjects, 61% were females (11/18) and 39% were males (7/18). The majority of subjects were Caucasian (16/18, 89%) and 2/18 (11%) subjects were of European/Middle Eastern ethnicity. The mean age and weight of the 18 subjects were 24 years (range, 19-36 years) and 72 kg (range, 60-95 kg), respectively.

D4T Formulation and Dose/Lot Number/Expiration Date/Batch Size (when available)

- Zerit™: 1 x 40-mg capsule/Lot # MLS37/November 2001
- Over-encapsulated Zerit™: 1 x 40-mg capsule/Lot # TP-0037-00072-0089/. [redacted] capsules

PK Sampling Scheme

Serial blood samples for assay of plasma concentrations of d4T were collected on Day 1 at the following times for each treatment period: pre-dose (time 0) and then 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours post-dose.

PK Analysis

- Plasma d4T concentration-time data for each subject were analyzed by noncompartmental methods, using WinNonlin, Professional version 3.0.
- The following PK parameters were calculated based on d4T plasma concentration-time data: C_{max}, t_{max}, AUC_{0-t}, $t½$, $AUC_{0-\infty}$, CL/F, and V_z/F
- All PK parameters except for t_{max} were log transformed before statistical analyses. SAS, version 6.12 was used to compare the two treatments
- 90% CI for the geometric least squares mean ratio of Treatment B vs. Treatment A were constructed
- Treatments were considered no different with respect to AUC and C_{max} if the result of the 90% CI of the ratio was within the range of 0.80 and 1.25

D4T Assay/Analytical Method

A validated [redacted] bioanalytical method was used to determine d4T concentrations in plasma.

Study plasma samples were analyzed with 7 calibration standards (analyzed in duplicate) and 4 QC samples (analyzed in duplicate) per analytical run. Correlation coefficients were all greater than 0.983. Inter-day precision, expressed as %CV, ranged

from 6.0% to 8.0% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from
-2.8% to 2.1% for the human plasma assay. The lower limit of quantitation (LLOQ) for d4T was —ng/mL.

FTC-113 Study Results

Table 1 provides the d4T arithmetic mean (%CV) PK parameter estimates by treatment and Table 2 provides the d4T BE statistical results of treatment comparisons.

Table 1. 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)	$t_{1/2}$ (h)
Zerit™ (40-mg capsule) (N=18)	Mean	0.834	0.81	2.05	2.11	1.74
	%CV	24	33	14	14	15
Zerit™ (over-encapsulated, 40-mg) (N=18)	Mean	0.766	0.92	2.03	2.09	1.78
	%CV	18	40	14	14	16

Table 2. 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	0.988
				90% CI	0.943, 1.035
C_{max} (µg/mL)	Geom. Mean	0.81	0.75	GLS Ratio	0.924
				90% CI	0.831, 1.028

Reviewer Comment: The PK parameter estimates are similar for the two d4T formulations. The d4T over-encapsulated formulation is BE to the d4T capsule formulation.

Conclusion

- 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

6.2 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-500	Brand Name	
OCPB Division (I, II, III)	DPEIII	Generic Name	Emtricitabine
Medical Division	Anti-Virals	Drug Class	NRTI
OCPB Reviewer	Jennifer L. DiGiacinto	Indication(s)	Treatment of HIV-1
OCPB Team Leader	Kellie S. Reynolds	Dosage Form	Capsule
		Dosing Regimen	200 mg QD
Date of Submission	03September2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	03July2003	Sponsor	Gilead Pharmaceuticals
PDUFA Due Date		Priority Classification	1S
Division Due Date			

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.	X	18	13	
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	X	1 (FTC-106)	1	Complete recovery of single 14C-emtricitabine dose was achieved within 7-days (86% U and 14% F)
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	PDM-037 (in vitro study demonstrated < 4% of protein binding for all species studied: Rabbit, Monkey, Human, Rat)
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	FTC-106 (mass balance)
multiple dose:	X	1	1	FTC-106 (mass balance)
Patients-				
single dose:	X	1	0	143-001
multiple dose:	X	2	1	FTC-101 and FTC-303 (PK sub-study)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4	4	FTC-103, FTC-104, FTC-108, FTC-114 (ZDV, d4T, IDV, EMV, FCV, and TDF)
In-vivo effects of primary drug:	X	4	4	FTC-103, FTC-104, FTC-108, FTC-114 (ZDV, d4T, IDV, EMV, FCV, and TDF)
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:	X	1	0	FTC-105
geriatrics:				
renal impairment:	X	1	1	FTC-107
hepatic impairment:				
PD:				
Phase 2:	X	2	1	FTC-101(14-day) and FTC-102 (10-day) vs. 3TC
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:	X	1	1	FTC-110 studied relative and absolute BA using capsule, solution, and IV solution
Relative bioavailability -				
solution as reference:	X	1	1	FTC-110 studied relative and absolute BA using capsule, solution, and IV solution
alternate formulation as reference:	X	1	1	FTC-110 studied relative and absolute BA using capsule, solution, and IV solution
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	2	FTC-109 (Pilot), FTC-110, and FTC-111 (Pivotal)
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	FTC-111 had a food-effect arm for the 200-mg capsule
Dissolution:	X	1	1	Capsule : Q= % in 30 minutes for
(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				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not 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	

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

/s/

Jennifer DiGiacinto
7/2/03 10:39:03 AM
BIOPHARMACEUTICS

Jenny Zheng
7/2/03 11:22:19 AM
BIOPHARMACEUTICS

Kellie Reynolds
7/2/03 12:27:04 PM
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