OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-896	Submission Date(s): March 29, 2005
Brand Name	EMTRIVA® Oral Solution
Generic Name	Emtricitabine Oral Solution (10-mg/mL)
Reviewer	Jennifer L. DiGiacinto, Pharm.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVDP
Sponsor	Gilead®
Relevant IND(s)	IND 53,971
Submission Type; Code	505 (b) (1), 1P
Formulation; Strength(s)	Oral Solution (10-mg/mL)
Dosing regimen	6-mg/kg QD up to a 240-mg maximum daily dose for pediatric patients. 240-mg QD for adults $\geq$ 18 years of age.
Indication	Treatment of HIV-1 infection.

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1. Executive Summary

Emtricitabine (FTC) is nucleoside reverse transcriptase inhibitor (NRTI) that is currently approved as a 200-mg capsule formulation and marketed as EMTRIVA® Capsule and as a fixed dose combination with tenofovir disoproxil fumarate (TDF) and marketed as TRUVADA® for the treatment of HIV infection in adults at least 18 years of age. The applicant developed a new oral solution (10-mg/mL) (EMTRIVA® Oral Solution) and studied this formulation in HIV-infected pediatric patients between the ages of 3-months and 17 years of age. In support of this NDA, the applicant adequately addressed the following issues:

- Determined the relative bioavailability (BA) of oral FTC, administered as 200-mg of the FTC oral solution formulation and compared to a 200-mg FTC oral capsule (FTC-110).
- Determined the absolute BA of oral FTC, administered as a solution formulation, when compared to an IV dose of FTC (FTC-110).
- Determined there is no clinically significant food effect observed with the oral solution regardless of the content of the meal (high-fat or light meal) (GS-US-162-0101).
- Determined the single dose and steady-state FTC concentrations in HIV-1 infected pediatric subjects and identified an FTC dose (for the capsule and the oral solution) that achieves plasma concentrations comparable to those in adults given 200-mg FTC once daily (FTC-105, FTC-203, FTC-202, and FTC-211).

1.1 Recommendation

The clinical pharmacology and biopharmaceutics information submitted to NDA 21-896 is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to this submission.

1.2 Post Marketing Commitments

None.

1.3 Summary of Important Clinical Pharmacology & Biopharmaceutics Findings

FTC Oral Solution will be administered once daily as part of an antiretroviral regimen to HIV-1 infected pediatric subjects $\geq$ 3-months of age who are unable to swallow an intact capsule and to HIV-infected adults who are unable to swallow an intact capsule or who need FTC dosing adjustments due to renal impairment. This NDA contains an absolute and relative BA study (FTC-110), a food effect study (GS-US-162-0101), a single-dose pharmacokinetic (PK) study in HIV-infected pediatric subjects (FTC-105), and three long term safety, PK, and antiviral activity studies conducted in HIV-1 infected pediatric subjects (FTC-203, FTC-202 (PACTG1021), and FTC-211).

FTC-110 determined the absolute BA of the oral FTC, administered as a liquid solution and determined the relative BA of oral FTC, administered as the 200-mg oral capsule formulation, when compared to the oral solution formulation of FTC.

The results of FTC-110 demonstrate that the absolute BA of the FTC oral solution formulation is 75%, which was an unexpected finding. The absolute BA of the FTC capsule was 93%. In addition, the BA of the 200-mg FTC capsule formulation relative to the oral solution formulation was 124%. See the summary data for the absolute and relative BA study below.

Table 1. Summary of FTC BA Estimates for Study FTC-110-Results of Statistical Analysis (N=12)

Statistic	Treatment Comparison		
	Capsule/Solution	Capsule/IV	Solution/IV
$AUC_{0-\infty}$ (µg•h/mL)			
GLS Mean Ratio	1.244	0.929	0.746
90% CI	1.166-1.327	0.781-0.990	0.700-0.796
AUC_{0-t} (µg•h/mL)			
GLS Mean Ratio	1.279	0.924	0.723
90% CI	1.198-1.365	0.866-0.987	0.677-0.771
C_{max} (µg/mL)			
GLS Mean Ratio	1.533	0.561	0.366
90% CI	1.418-1.657	0.519-0.607	0.339-0.396

Study GS-US-162-0101 investigated the food effect for the FTC oral solution when administered with a high fat meal and a low fat/caloric meal. This was a randomized, open-label, single-center, single-dose, three-way crossover study with a minimum 7-day washout interval between successive treatments. The results of this food effect study demonstrate the administration of FTC oral solution with food has no effect on the C_{max} or AUC of FTC, but appeared to delay the time to maximum concentration of FTC. This delay in t_{max} is not clinically significant. See the summary data for the food effect study below.

Table 2. Statistical Analysis of FTC Oral Solution PK Parameter Estimates by Treatment

Statistic	Treatment			Statistic	Treatment Comparison	
	A (Fasted)	B (High Fat)	C (Low Fat)		B vs. A	C vs. A
AUC_{0-inf} (µg·h/mL)						
Geo LS Mean	10.20	10.73	10.44	**Geo LS Mean Ratio**	1.052	1.024
				90% CI (Lower)	1.007	0.980
				90% CI (Upper)	1.099	1.070
AUC_{0-last} (µg·h/mL)						
Geo LS Mean	9.53	10.23	9.96	**Geo LS Mean Ratio**	1.073	1.044
				90% CI (Lower)	1.021	0.993
				90% CI (Upper)	1.128	1.098
C_{max} (µg/mL)						
Geo LS Mean	1.571	1.517	1.636	**Geo LS Mean Ratio**	0.966	1.042
				90% CI (Lower)	0.898	0.969
				90% CI (Upper)	1.039	1.121
t_{max} (h)						
LS Mean	1.21	2.33	1.86	**LS Mean Ratio**	1.931	1.541
				90% CI (Lower)	1.637	1.247
				90% CI (Upper)	2.225	1.835

Source: Section 15; Table 7 GS-US-162-0101 Study Report

FTC-105, a single-dose pediatric PK study, identified a pediatric dose of FTC (6-mg/kg QD) to take forward into long term Phase II safety and PK trials. Three long term Phase II safety, PK, and antiviral activity trials were conducted in pediatric patients (3-months to 17 years of age) administering the 6-mg/kg dose of FTC as part of an antiretroviral multi-drug regimen (FTC-203, FTC-202 (PACTG1021), and FTC-211). A combined analysis was conducted of the 77 HIV-infected pediatric subjects ranging from 3 months to 17 years of age who had PK data collected between Week 2 and Week 4 while enrolled in one of the three studies. The results from FTC-105 and the three Phase II safety and PK studies provide adequate data to establish FTC dosing guidelines for pediatric patients (3 months to 17 years of age).

FTC PK parameter estimates are summarized in Table 3 below by age group for all subjects and Table 4 by age group for subjects who received the oral solution formulation. Table 5 below summarizes the PK results of three steady-state studies in adults who took 200-mg FTC daily.

Table 3. Phase 2 Studies: Mean (%CV) Values for FTC PK Parameters at Steady-State by Age Group for Subjects Receiving Capsules and Solution (6-mg/kg, Maximum Capsule Dose 200-mg and Maximum Oral Solution Dose 240-mg)

Age Group	N		C_{max} (µg/mL)	C_{min} (µg/mL)	t_{max} (hr)	AUC_{tau} (hr•µg/mL)	$t_{1/2}$ (hr)	CL/F (mL/min/kg)
1 3–24 mo	14[a]	Mean CV%	1.93 34	0.059 52	1.6 54	8.70 37	8.87 36	13.2 34
2 25 mo–6 yr	19	Mean CV%	1.91 38	0.059 71	1.6 62	9.03 33	11.29 57	13.0 46
3 7–12 yr	17	Mean CV%	2.72 30	0.066 45	1.7 99	12.57 28	8.19 39	8.4 54
4 13–17 yr	27	Mean CV%	2.73 31	0.064 94	1.7 65	12.55 43	8.94 37	6.4 45

[a] Subject 0104 (Study-FTC-203) was excluded from the summary statistics
Source: Appendix 2.7.2.5, Table 2.7.2.5

Table 4. Phase 2 Studies: Mean (%CV) Values for FTC PK Parameters at Steady State by Age Group for Subjects Receiving Oral Solution (6-mg/kg, Maximum Oral Solution Dose 240-mg)

Age Group	N		Cmax (µg/mL)	Cmin (µg/mL)	tmax (hr)	AUCtau (hr·µg/mL)	t1/2 (hr)	CL/F (mL/min/kg)
1 3–24 mo	14	Mean CV%	1.93 34	0.059 52	1.6 54	8.70 37	8.87 36	13.2 34
2 25 mo–6 yr	19	Mean CV%	1.91 38	0.059 71	1.6 62	9.03 33	11.29 57	13.0 46
3 7–12 yr	7	Mean CV%	2.64 37	0.057 49	1.3 38	11.01 37	8.60 35	11.21 55
4 13–17 yr	1	Mean CV%	3.84 —	0.046 —	1.0 —	14.83 —	10.59 —	7.83 —

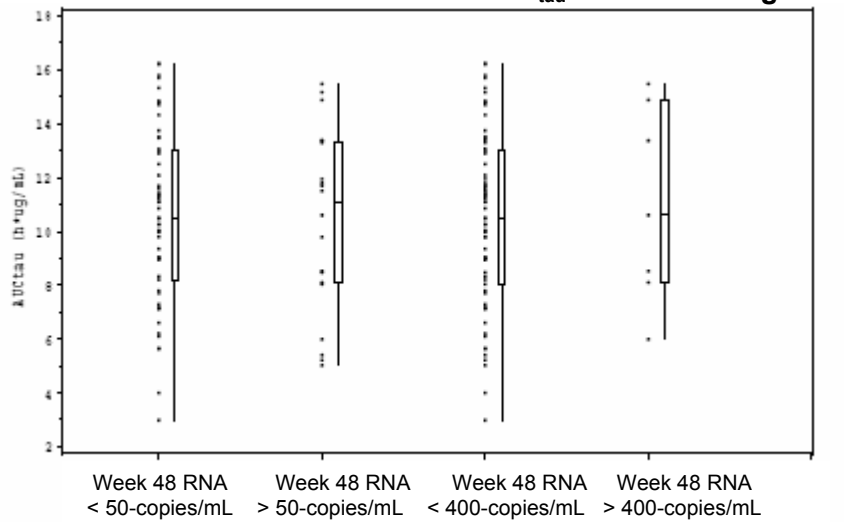
Source: Appendix 2.7.2.5, Table 2.7.2.8

Table 5. Summary of Mean (%CV) Steady-State PK Parameter Estimates in Adults for FTC Following 200-mg Once Daily Dose

Clinical Study (Protocol) No.	Subjects Number (M/F)Type Age: mean (range)	C_{max} (µg/mL)	t_{max} (hr)	C_{min} (µg/mL)	AUC_{tau} (hr•µg/mL)	t1/2 (hr)	CL/F (mL/min)
FTC-101	8 (8M/0F) HIV-infected subjects 37 (29–42) yr	1.72 (53%)	2.00 (48%)	0.05 (24%)	8.00 (15%)	8.24 (31%)	425 (15%)
FTC-106	5 (5M/0F) Healthy volunteers 37 (33–42) yr	1.72 (16%)	1.00 (0%)	0.07 (28%)	10.04 (18%)	10.2 (19%)	339 (20%)
FTC-303	12 (1M/11F) HIV-infected subjects 38 (21–61) yr	1.94 (24%)	1.80 (58%)	0.11 (71%)	11.31 (29%)	8.08 (32%)	317 (27%)

The distribution of AUC_{tau} values versus virologic response ($\leq$ 400 copies/mL and $\leq$ 50 copies/mL) is presented in Figure 1 below as a combined analysis of all three Phase II studies.

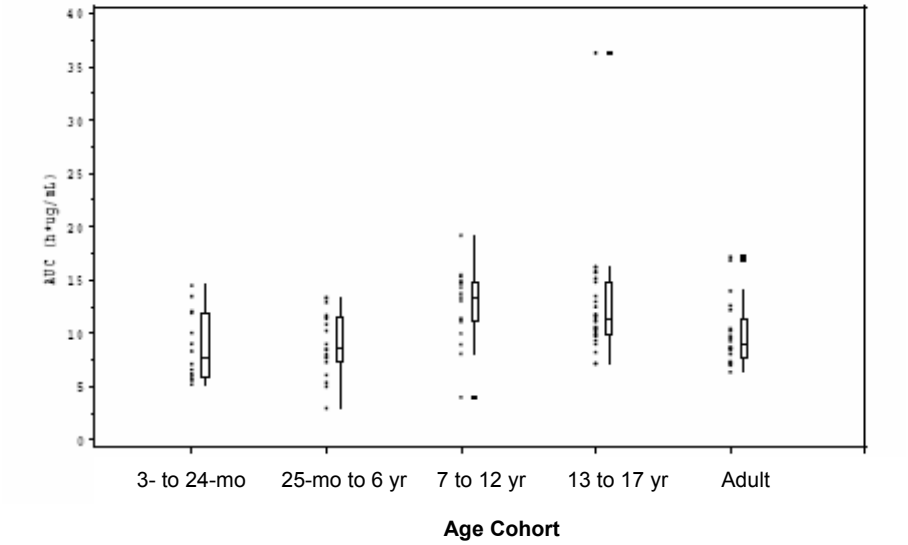
Figure 1. Phase 2 Studies: Distribution of AUC_{tau} versus Virologic Response



The mean AUC_{tau} value for the 20 HIV-infected adults in studies FTC-101 and FTC-303 is 10.0 µg·h/mL (CV=31%, range 6.4-17.2 µg·h/mL). The corresponding mean C_{max} for the same group of adults was 1.85 µg/mL (CV-36%, range 0.890-3.720 µg/mL). For the pediatric Age Groups 1 and 2 (3 months to 6 years of age) the mean AUC_{tau} value was approximately 9 µg·h/mL. For children age 7 years and older, the mean AUC_{tau} value was slightly higher than in adults receiving 200-mg QD (mean AUC_{tau} for subjects in Age Group 3 and 4 (7 to 18 years) was 12.5 µg·h/mL, approximately 11% higher than FTC-303, a pivotal efficacy study in adults).

Although the mean AUC_{tau} values were slightly higher in the older children, the values for all age groups fell within the range seen in adults. This is illustrated in Figure 2 below where the distribution of AUC_{tau} values by age group of pediatric subjects receiving FTC 6-mg/kg QD and 20 adults receiving 200-mg FTC QD are depicted.

Figure 2. Distribution of AUC (µg·h/mL) by Age Cohort



In summary:

- Adequate number of subjects was studied to characterize the PK in children 3 months of age up to 17 years of age.
- The FTC AUC_{tau} achieved in children receiving a 6-mg/kg daily dose up to a maximum of 240-mg with the solution and up to a maximum of 200-mg with the capsule is similar to exposures achieved in adults receiving a 200-mg capsule daily.
- Younger children had higher variability in PK compared to adults. This may be due to a greater variability in drug clearance or perhaps due to the difficulties associated with dosing liquid formulations to young children.
- Based on the Phase 2 study results and the relative BA of the oral solution to the capsule, the pediatric dosing recommendation is:
    - FTC oral solution: 6-mg/kg QD up to a maximum dose of 240-mg daily
    - FTC capsule: 1 x 200-mg capsule QD for children > 33 kg who can swallow an intact capsule.

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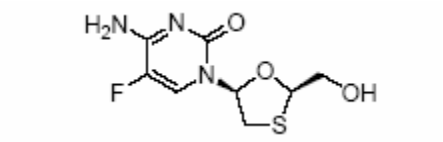
2. QUESTION BASED REVIEW (See NDA 21-500 and NDA 21-356 for section 2.1 through 2.4 information)

2.1 General Attributes of the Drug

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

The FTC oral solution contains FTC as the active ingredient. Chemically, FTC is 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. The chemical structure, molecular formula and formula weight of FTC are shown below.



Emtricitabine
$C_8H_{10}FN_3O_3S$
m.w. 247.24

FTC oral solution is a clear, orange to dark orange liquid in a buffered, flavored, aqueous formulation for oral administration. Each mL of FTC oral solution contains 10 mg of FTC. FTC oral solution is packaged in (b) (4) amber (b) (4) bottles with (b) (4) child resistant caps. Each bottle is filled to provide a deliverable volume of 170 mL of FTC oral solution.

Table 6. Quantitative Composition of EMTRIVA® Oral Solution,(10 mg/mL).

Component	Reference to Quality Standard	Function	Quantity per 100 mL
Emtricitabine	In-house standard		(b) (4)
Cotton Candy Flavor (b) (4)	In-house standard		
Edetate Disodium	USP		
FD&C Yellow No. 6	21 CFR 82.706		
Hydrochloric Acid	NF		
Methylparaben	NF		
Monobasic Sodium Phosphate	USP		
Propylene Glycol	USP		
Propylparaben	NF		
Purified Water	USP		
Sodium Hydroxide	NF		
Xylitol	NF		

1 The quantity used is adjusted on the basis of the purity (drug content factor) of each batch of emtricitabine drug substance.
2 Quantity noted is the dihydrate form.
3 Used to prepare (b) (4) hydrochloric acid solution to adjust solution pH to 7.2, as needed.
4 Quantity noted is the (b) (4).
5 Used to prepare (b) (4) sodium hydroxide solution to adjust solution pH to 7.2, as needed.

2.1.2 What are the proposed dosage(s) and route(s) of administration?

For pediatric patients (3 months through 17 years of age) the dose of EMTRIVA® is:

- **EMTRIVA® Oral Solution:** 6-mg/kg up to a maximum of 240 mg (24 mL) of the oral solution administered by mouth once daily.
- **EMTRIVA® Capsule:** For children weighing > 33 kg who can swallow an intact capsule, one 200-mg capsule administered by mouth once daily.

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical studies used to support dosing or claims?

The applicant collected the important PK, efficacy, and safety information in the following clinical trials:

Phase II clinical trials
FTC-203: An Open-Label Study of a Once Daily Dose of FTC in Combination with Other Antiretroviral Agents in HIV-Infected Pediatric Subjects (N=116).

FTC-202: An Open-Label Study to Evaluate the Safety, Tolerance, Antiviral Activity and Pharmacokinetics of FTC in Combination with Efavirenz and Didanosine in a Once Daily Regimen in HIV-Infected Antiretroviral Therapy Naïve or Very Limited Antiretroviral Exposed Pediatric Subjects (PACTG1021) (N=37).

FTC-211: An Open-Label Study of a Once-Daily Dose of FTC in Combination with Other Antiretroviral Agents in HIV-Infected Pediatric Subjects (N=16).

FTC-203
This is an ongoing (> 96 weeks), multi-center, open-label, non-randomized Phase II clinical study designed to evaluate the safety, antiretroviral activity, and PK of FTC in combination with other antiretroviral agents. The study was designed to enroll approximately 60 to 120 HIV-1 infected antiretroviral naïve and experienced pediatric subjects between the ages of 3 months and 17 years of age, separated in the following age groups (N=PK subjects):

- Group 1: 3 months to 24 months (N=14)
- Group 2: from 25 months to 6 years of age (N=9)
- Group 3: from 7 years to 12 years of age (N=9)
- Group 4: from 13 years to 17 years of age (N=3)

- Naïve subjects received 6-mg/kg FTC (up to a maximum of 200-mg QD for the capsule and up to a maximum of 240-mg QD when using the oral solution) + stavudine (d4T) (1-mg/kg BID if < 30-kg, 30-mg BID if 30 to 59 kg; 40-mg BID if $\geq$ 60 kg) + lopinavir/ritonavir (LPV/RTV) (12/3-mg/kg BID if $\geq$ 7 to < 15 kg; 10/2.5 mg/kg BID if $\geq$ 15 to $\leq$ 40 kg; 400/100 mg if > 40 kg).
- Experienced subjects: Replaced the 3TC in their existing antiretroviral regimens with FTC (up to a maximum of 200-mg QD for the capsule and up to a maximum of 240-mg QD when using the oral solution). At the investigator's discretion, one or more of the subject's background medications could be replaced at the same time 3TC was replaced.

FTC-202 (PACTG1021)
This is an ongoing (Treatment duration extends up to 192 weeks), open-label, non-randomized trial designed to evaluate the safety, tolerance, antiviral activity, and PK of FTC when combined with efavirenz (EFV) and didanosine (ddI) in a fully once daily regimen in HIV-infected antiretroviral therapy naïve or very limited antiretroviral exposed pediatric subjects. Enrollment in the two oldest age groups (N=37) was completed in October 2002, which included (N=PK subjects):

- Group 2: from 3 years to 12 years of age (N=17)
- Group 3: from 13 years to 21 years of age (N=14)

Subjects who were > 17 years of age were not included in the combined PK analysis. Additionally, Group 1 (N=16) will start enrolling subjects once the EFV dose has been established for subjects from 3 months to < 3 years of age.

All subjects received a triple drug regimen comprised of:

- FTC 6-mg/kg QD up to a maximum of 200mg QD (regardless of formulation administered) + ddI 240-mg/m^2 QD (up to a maximum of 400-mg QD) + EFV (based on body weight up to a maximum of 600-mg QD as a capsule or up to 720-mg QD as an oral solution).

FTC-211
This was a 48-week, open-label, non-randomized clinical study designed to evaluate the safety, PK, and antiretroviral activity of FTC containing regimens in naïve and experienced HIV-1 infected pediatric subjects. Depending on their age, HIV-1 infected pediatric subjects < 18 years of age were to receive one of two FTC containing regimens. Sixteen subjects were enrolled into the following age groups (N=PK subjects):

Group 2: 7 to 12 years of age (N=1)
Group 3: 13 to 17 years of age (N=15)

- Naïve and experienced patients received FTC (up to a maximum of 200-mg QD for the capsule and up to a maximum of 240-mg QD when using the oral solution) + ddI (240-mg/m^2 up to a maximum of 400-mg daily) + EFV (based on body weight up to a maximum of 600-mg QD as a capsule or up to 720-mg QD as an oral solution).

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

The surrogate efficacy endpoints for HIV-1 infection are plasma HIV viral load (HIV-RNA) and CD4 cell counts. The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for FTC-203, FTC-202, and FTC-211 were the proportion of subjects at Week 48 with suppression of plasma HIV-RNA to below the LLOQ for the assay, i.e., $\leq$ 400-copies/mL and $\leq$ 50-copies/mL for the Standard and Ultra Sensitive Tests, respectively.

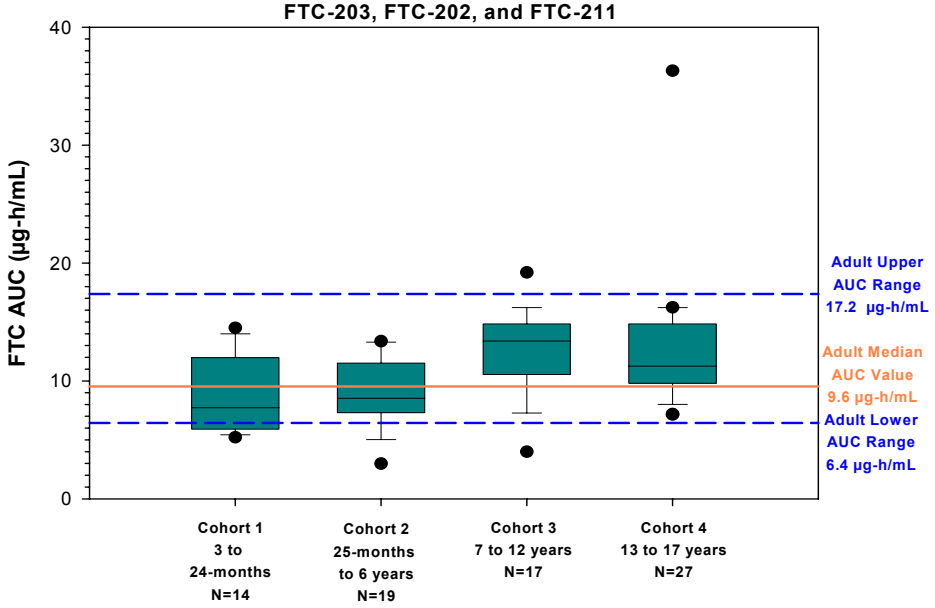
2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

FTC concentrations in human plasma and human urine samples were determined by validated liquid chromatographic methods using LC/MS/MS for plasma and solid phase extraction followed by LC/MS for urine samples or dilution of the urine followed by direct injection onto LC/MS/MS. The assays are acceptable. No active metabolites are present in the plasma; however, the active FTC intracellular metabolite is FTC-5'-TP.

2.2.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The FTC dose is based on similar exposures observed in adults in pivotal clinical trials. See Figure 3 below. There are no unresolved dosing or administration issues.

Figure 3. EMTRIVA Oral Solution and Capsule AUC Comparisons Across Cohorts for Pediatric Patients Enrolled into FTC-203, FTC-202, and FTC-211

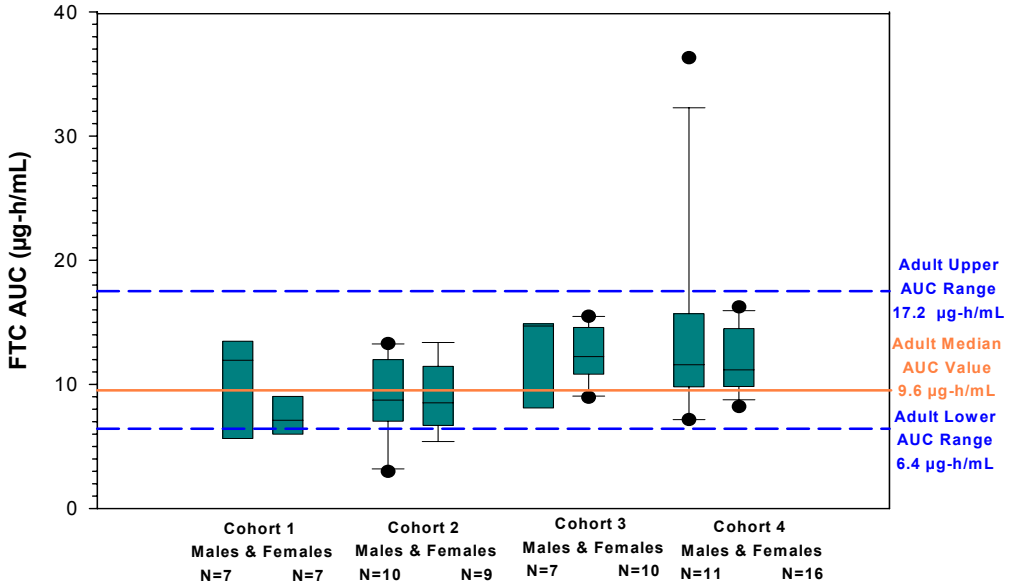


2.3 Intrinsic Factors

2.3.1 Gender

An evaluation of steady-state plasma FTC AUC concentrations from FTC-203, FTC-202, and FTC-211 does not indicate a gender difference exists for pediatric subjects who received either formulation of FTC. See Figure 4 below.

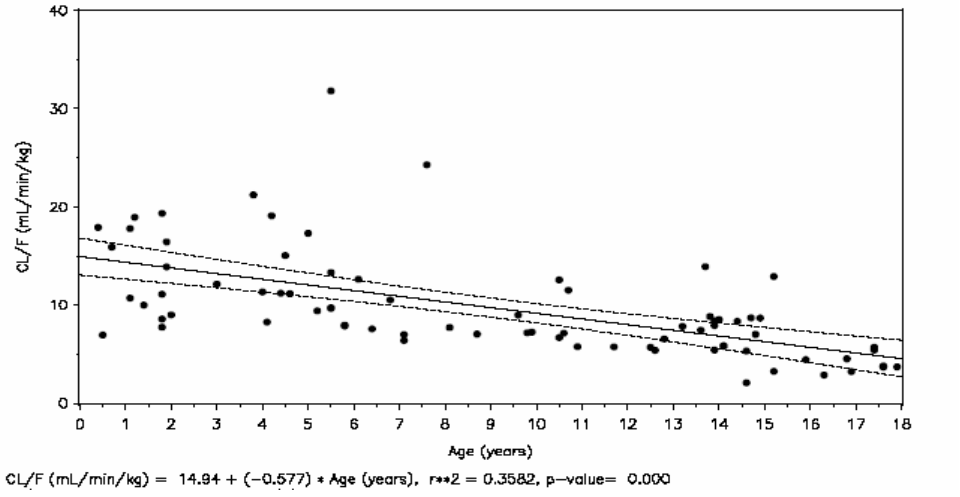
Figure 4. EMTRIVA AUC Comparisons by Gender and Age for Pediatric Subjects Enrolled into FTC-203, FTC-202, and FTC-211.



2.3.2. Age

The relationship of apparent total clearance (CL/F) weight normalized vs. age is presented in Figure 5 below.

Figure 5. Phase 2 Studies: CL/F vs. Age for Weight- Normalized CL/F



Mean CL/F values (mL/min) increases with increasing age. However, CL/F normalized for weight (mL/min/kg) decreases with age. Adult CL/F (weight normalized) values are reached at approximately age 14. This difference in CL/F accounts for the higher exposures seen in the older pediatric subjects.

2.3.3 Renal Impairment

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

- FTC is rapidly and extensively absorbed orally with little or no first-pass metabolism and high (93%) oral BA for the capsule and (75%) oral BA for the oral solution.
- FTC shows low inter-subject variability in its PK parameter estimates.
- FTC is primarily eliminated via renal excretion (60 -70% of an oral dose) with metabolism as a minor elimination pathway (< 13% of an oral dose).

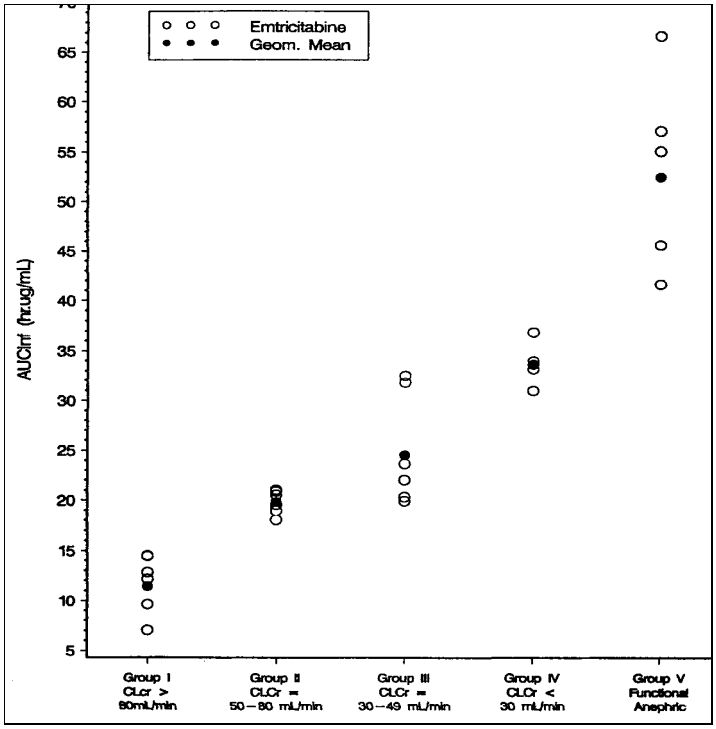
EMTRIVA® Oral Solution may be administered to patients with varying degrees of renal impairment. The current dosing recommendations for the FTC capsule recommend modifying the dosing interval. The FTC oral solution allows administration of doses less than 200-mg, so it is possible to give a lower dose once daily. The renal impairment dosing recommendations will be updated in the product label to reflect the dosing adjustments for both formulations (See Below).

Table 7. Proposed Renal Impairment Dosing in Adults with the FTC Capsule and FTC Oral Solution

Formulation	> 50 mL/min	30-49mL/min	29-15 mL/min	< 15-mL/min or on hemodialysis
Capsule	200-mg QD	200-mg Q48H	200-mg Q72H	200-mg Q96H
Oral Solution	240-mg QD (24 mL)	120-mg QD (12 mL)	80-mg QD (8 mL)	60-mg QD (6 mL)

Reviewer Note: EMTRIVA® Oral Solution provides patients with renal impairment an additional FTC dosing adjustment option. In FTC-107 (reviewed with NDA 21-500), subjects with varying degrees of renal impairment were administered a single 200-mg FTC capsule. Results from this study demonstrate that FTC 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. 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 of the degree of renal function. See Figure 6 below for a comparison of AUC values across the different groups of subjects from Study FTC-107.

Figure 6. Plots of FTC PK Parameter Estimates across Groups (Study FTC-107)



This figure illustrates AUC values for FTC are linear as renal function (CL_{cr}) decreases.

At the time of the EMTRIVA® Capsule NDA submission, the applicant provided justification for grouping the subjects with CL_{cr} values of 50 to < 80-mL/min (mild renal impairment) with subjects with normal renal function. The justification stated that no dose related adverse events were identified in study FTCB-101 patients who received FTC 300-mg QD for 8-weeks. Because FTC PK are dose-proportional, the 300-mg dose provides approximately 1.5-fold the exposure of the 200-mg dose, which is similar to the drug levels expected in subjects with a CL_{cr} of 50 to 80 mL/min. Therefore; FTC dosing interval adjustments apply to patients with a CL_{cr} value of 49-mL/min or less.

The proposed renal impairment dosing adjustments for EMTRIVA® Oral Solution follow the original recommendations but rather than altering the dosing interval, a lower FTC dose will be given daily making this a simpler regimen. This approach is acceptable because FTC displays linear PK, and similar exposure (AUC) is expected based on principles of superposition. The oral solution dose is adjusted based on relative BA.

Extrinsic Factors-
Not Applicable.

2.4 General Biopharmaceutics

2.5.1. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The proposed to-be-marketed EMTRIVA® Oral Solution formulation (Formulation C-1) was used in the Phase II studies (See Table Below).

Table 8. FTC Oral Solution (10-mg/mL) Formulation Development Summary

Formulation Code	Clinical Study (Protocol #)	Formulation or Manufacturing Change	Effect of Change
Formulation A	FTC-105	• Initial clinical formulation poor stability at room temperature	NA
Formulation C (b) (4) Cotton Candy Flavoring	FTC-203 (approximately 5 patients received this formulation before Formulation C-1 was available)	• Reformulated to improve stability. • (b) (4) • •	No impact on BA expected
Formulation C-1 Cotton Candy Flavor	FTC-110 FTC-203 FTC-211 FTC-202 GS-US-162-01010	• Reduced paraben levels • pH adjusted to 7.2 to enhance stability	No impact on BA expected

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

Study GS-US-162-0101 investigates the food effect for the FTC oral solution when administered with a high fat meal and a low fat/caloric meal. This was a randomized, open-label, single-center, single-dose, three-way crossover study with a minimum 7-day washout interval between successive treatments. The results of this food effect study demonstrate the administration of FTC oral solution with food has no effect on the C_{max} or AUC of FTC , but appeared to delay the time to maximum concentration of FTC. This delay in t_{max} is not considered to be of any clinical significance. See the summary data for the food effect study below.

Table 9. Statistical Analysis of FTC Oral Solution PK Parameter Estimates by Treatment

Statistic	Treatment			Statistic	Treatment Comparison	
	A (Fasted)	B (High Fat)	C (Low Fat)		B vs. A	C vs. A
$AUC_{0\text{-}inf}$ (µg·h/mL)						
Geo LS Mean	10.20	10.73	10.44	**Geo LS Mean Ratio** **90% CI (Lower)** **90% CI (Upper)**	1.052 1.007 1.099	1.024 0.980 1.070
$AUC_{0\text{-}last}$ (µg·h/mL)						
Geo LS Mean	9.53	10.23	9.96	**Geo LS Mean Ratio** **90% CI (Lower)** **90% CI (Upper)**	1.073 1.021 1.128	1.044 0.993 1.098
C_{max} (µg/mL)						
Geo LS Mean	1.571	1.517	1.636	**Geo LS Mean Ratio** **90% CI (Lower)** **90% CI (Upper)**	0.966 0.898 1.039	1.042 0.969 1.121
t_{max} (h)						
LS Mean	1.21	2.33	1.86	**LS Mean Ratio** **90% CI (Lower)** **90% CI (Upper)**	1.931 1.637 2.225	1.541 1.247 1.835

Source: Section 15; Table 7 GS-US-162-0101 Study Report

2.5.3 Formulation

FTC-110 determined the absolute BA of FTC oral solution and determined the relative BA of FTC 200-mg oral capsule formulation compared to the oral solution formulation.

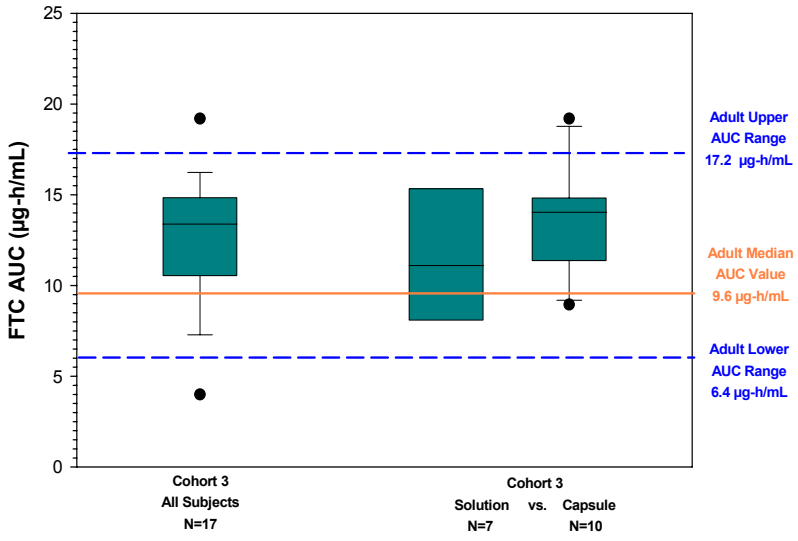
The results of FTC-110 demonstrate that the absolute BA of the FTC oral solution formulation is 75%, which was an unexpected finding. The absolute BA of the FTC capsule was 93%. In addition, the BA of the 200-mg FTC capsule formulation relative to the oral solution formulation was 124%. See the summary data for the absolute and relative BA study below.

Table 10. Summary of FTC BA Estimates for Study FTC-110-Results of Statistical Analysis (N=12)

Statistic	Treatment Comparison		
	Capsule/Solution	Capsule/IV	Solution/IV
$AUC_{0-\infty}$ (µg•h/mL)			
GLS Mean Ratio	1.244	0.929	0.746
90% CI	1.166-1.327	0.781-0.990	0.700-0.796
AUC_{0-t} (µg•h/mL)			
GLS Mean Ratio	1.279	0.924	0.723
90% CI	1.198-1.365	0.866-0.987	0.677-0.771
C_{max} (µg/mL)			
GLS Mean Ratio	1.533	0.561	0.366
90% CI	1.418-1.657	0.519-0.607	0.339-0.396

In the combined analysis for the Phase II studies, the study subjects in Cohort 3 were a combination of those receiving either the EMTRIVA® Capsule formulation or the EMTRIVA® Oral Solution formulation. Figure 7 shows the exposure comparisons between formulations for the study subjects in Cohort 3.

Figure 7. Cohort 3 AUC Comparisons with All Subjects, Solution vs. Capsule, and Gender vs. Formulation for Pediatric Subjects Enrolled into FTC-203, FTC-202, and FTC-211

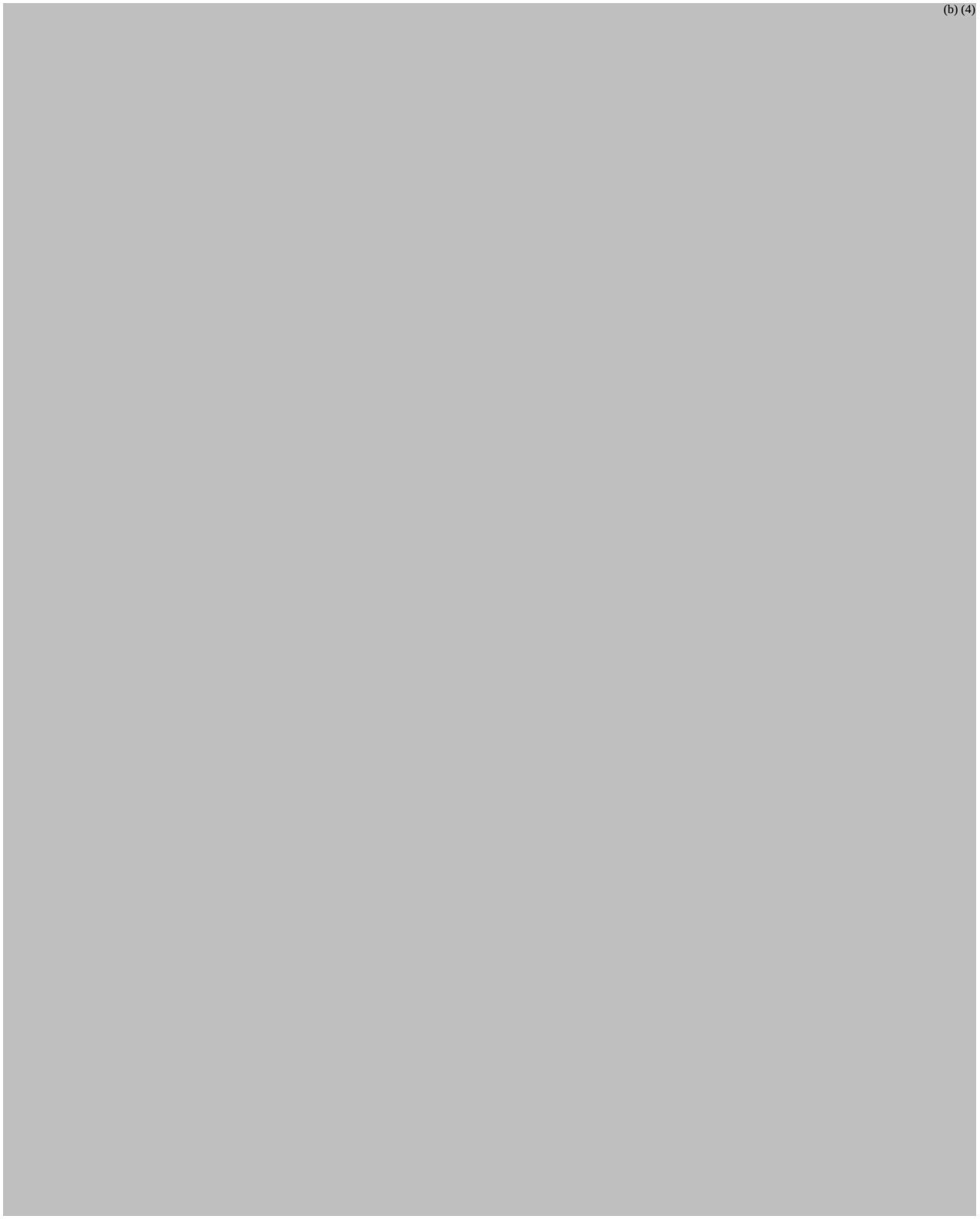


2.5 Analytical Section

Not Applicable (See individual study reviews).

3. Labeling Recommendations

(b) (4)



- **Emtriva Capsules:** for children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.

[redacted] (b) (4)

Dose Adjustment in Adult Patients with Renal Impairment

Formulation	> 50 mL/min	30-49mL/min	29-15 mL/min	< 15-mL/min or on hemodialysis
Capsule	200-mg QD	200-mg Q48H	200-mg Q72H	200-mg Q96H
Oral Solution	240-mg QD (24 mL)	120-mg QD (12 mL)	80-mg QD (8 mL)	60-mg QD (6 mL)

Although there are insufficient data to recommend a specific dose adjustment of EMTRIVA in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval similar to adult adjustments should be considered.

4. Appendices

4.1 Individual Study Reviews

4.1.1 Absolute and Relative Bioavailability Study

Title
FTC-110: A Study to Evaluate the Relative and Absolute Bioavailability of Emtricitabine in Healthy Volunteers.

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 $\geq$ 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. The average age and weight of the subjects were 32 years (range: 21-44 years) and 76.2 kg (range: 61.3-87.6 kg),

respectively. The 12 subjects had estimated CL_{cr} from 85 to 138 mL/min (mean: 113 mL/min).

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	(b) (4)	TP-0006-00205/November 2001
10-mg/mL FTC Oral Solution		TP-0006-00211/July 2001
10-mg/mL FTC IV Solution		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)

Reviewer Note*: The 200-mg capsule formulation and the 10-mg/mL oral solution are proposed commercial formulations.*

PK Sampling Scheme
Blood-
- No specific time points for sample collection were provided in the study report for the PK sampling. The report states 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 liquid chromatography/tandem mass spectrometry (LC/MS/MS) bioanalytical method was used to determine FTC concentrations in plasma and urine. (b) (4) , 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-inf} (µg•h/mL)	t½ (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
200-mg Solution n = 12	Mean	1.45	1.35	7.96	8.32	12.14	431	409
	%CV	15	30	16	16	18	25	15
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	Solution/IV
$AUC_{0-\infty}$ (µg•h/mL)			
GLS Mean Ratio	1.244	0.929	0.746
90% CI	1.166-1.327	0.781-0.990	0.700-0.796
AUC_{0-t} (µg•h/mL)			
GLS Mean Ratio	1.279	0.924	0.723
90% CI	1.198-1.365	0.866-0.987	0.677-0.771
C_{max} (µg/mL)			
GLS Mean Ratio	1.533	0.561	0.366
90% CI	1.418-1.657	0.519-0.607	0.339-0.396

- The absolute BA for FTC 200-mg capsule is 93%, which indicates 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, t_{max} and C_{max} values for the IV formulation are dependent on the rate and duration of the IV infusion.

- The absolute BA of the FTC oral solution formulation is 75%, which was an unexpected finding.
- The BA of the 200-mg FTC capsule formulation relative to the oral solution formulation was 124%.

Reviewer Comment: FTC oral solution formulation had a lower relative BA compared to the FTC oral capsule formulation. There is no difference in the rate of elimination of FTC when administered as a capsule or oral solution. As expected, the CL_R of FTC, which is the primary route of elimination of FTC, was nearly identical for all three treatments. The t_{max} values were similar for the capsule and oral solution (oral solution t_{max} was slightly less), which indicates a similar rate of absorption. The oral solution's C_{max} was substantially lower than the corresponding value for the capsule; therefore, the extent, but not the rate of FTC absorption from the oral solution is less than that of the capsule formulation. The reason for this finding is unknown. In addition, the oral solution formulation will be administered most often to pediatric patients and the exposures achieved with the oral solution formulation were used to select the pediatric dosing regimen.

Urinary Excretion Data

All 12 subjects had normal renal function, with an estimated CL_{cr} value > 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 Solution	200-mg IV Infusion
Total % Dose Excreted as FTC	Mean %CV	68.62 20	55.41 15	72.90 6
Average CL_R (mL/min)	Mean %CV	227.9 22	239.5 27	227.3 21
Ratio of CL_R:CL (IV) or CL_R:CL/F (oral)	Mean %CV	0.698 20	0.579 14	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 urinary excretion data collected in other FTC studies.

Conclusion

- The absolute BA of the 200-mg FTC capsule formulation is 93%.
- The absolute BA of the FTC oral solution formulation is 75%.
- The BA of the 200-mg FTC capsule formulation relative to the oral solution formulation is 124%.

4.1.2 Food Effect Study

Title
GS-US-162-0101: A Phase I, Open-Label, Randomized, Three-Way Crossover Study to Evaluate the Effect of Food on the Bioavailability of Emtricitabine Administered as EMTRIVA® Oral Solution in Healthy Volunteers.

A previous food effect study (administration of FTC after ingesting a standard high-fat meal) conducted with the FTC 200-mg capsule (FTC-111) demonstrated that although FTC C_{max} was decreased by 29% under fed conditions, there was no clinically significant effect on the bioavailability (BA) of FTC and the FTC 200-mg capsule could be taken with or without food. However, no study had explored the effect of food on the FTC oral solution formulation. Therefore, Study GS-US-162-0101 was conducted to evaluate the effect of food on the BA of FTC when administered as the oral solution, using both the standard high-fat meal recommended by the FDA and also a light meal with a lower fat content.

Study Design
This was a randomized, open-label, single-center, single-dose, three-way crossover study. Eligible subjects were randomized to receive each of the following three single-dose treatments over the course of three dose periods, with a minimum 7-day washout interval between successive treatments.

Study Treatments
- Treatment A: A single 20-mL dose of 10-mg/mL EMTRIVA® Oral Solution administered under fasting conditions (≥ 8 hours fast).
- Treatment B: A single 20-mL dose of 10-mg/mL EMTRIVA® Oral Solution administered at or within 5 minutes of consuming a standardized high-fat meal.
- Treatment C: A single 20-mL dose of 10-mg/mL EMTRIVA® Oral Solution administered at or within 5 minutes of consuming a standardized light (low-fat) meal.

The order each subject received the three treatments was determined by a randomization schedule based on a balanced Latin square design.

Test and Reference Product
- Each subject received 3 single 20-mL (200-mg) doses of 10-mg/mL EMTRIVA® Oral Solution (Batch No. TP-0006-03003 and theoretical batch size = (b) (4)).

Meal Composition

Standard High-Fat Meal Composition (Total Kcal = 793)

Carbohydrate	57.56 g	230 kcal
Protein	31.5 g	126 kcal
Fat	48.6 g	437 kcal

Standard Low-Fat Meal Composition (Total Kcal = 361)

Carbohydrate	61.3 g	245 kcal
Protein	10.6 g	42 kcal
Fat	8.2 g	74 kcal

Demographics

GS-US-162-0101 Study Subjects Demographics

Characteristics:	**Pharmacokinetic (N=18)**	
	N	**%**
Gender:		
Female	11	61.1
Male	7	38.9
Race:		
White	17	94.4
Black	1	5.6
Age (years):		
Mean (± SD)	29.4 (± 9.2)	
Min, Max	19, 44	
Weight (kg):		
Mean (± SD)	70.5 (± 10.3)	
Min, Max	53.1, 93.9	
Estimated CL_{cr} (mL/min):		
Mean (± SD)	126.7 (± 18.9)	
Min, Max	100.6, 154.3	

Source: Section 15; Table 1 GS-US-162-0101 Study Report

Pharmacokinetic (PK) 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, 24, 36, and 48 hours post-dose.

PK Data Analysis

All PK parameters were analyzed using analysis of variance (ANOVA). The primary analysis was based on log transformed PK parameters except for t_{max}. SAS™ (Version 6.12) PROC MIXED was used to compare treatments. A conclusion of no significant PK difference between the test and reference treatments was made if the 90% CI for the geometric least square mean ratio of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} were contained within the interval of 80-125%. The PK parameters of interest for assessing differences in BA were $AUC_{0\text{-last}}$, $AUC_{o\text{-inf}}$, and C_{max}. Other PK parameters were also examined but not used as criteria to determine lack of food effect: CL/F, λ_z, V_z/F, and t½.

GS-US-162-0101 Assay Validation

A validated LC/MS/MS bioanalytical method was used to assay FTC plasma samples. The assay is acceptable. The assay characteristics for FTC-111 are listed below.

Parameter	**Observation**
Linear Range	5 ng/mL - 2000 ng/mL
LLOQ	5 ng/mL
Stability (freeze-thaw)	Stable for 320 days when frozen at $^{-}80^{o}$ C
Specificity	Chromatograms provided and show no interference
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
Bias = -3.6% to76.2%	%CV = 2.6% to 8.2%	Bias = -2.6% to 4.9%	%CV = 3.7% to 7.2%

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

GS-US-162-0101 Study Results

The summary statistics of FTC pharmacokinetic parameters are listed below:

Descriptive Statistics for FTC Oral Solution PK Parameter Estimates by Treatment (N=18)

TX FTC Sol'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)
A: 200-mg Fasted	Mean	1.610	1.21	9.63	10.29	17.26	330	494
	%CV	25	32	15	14	21	13	26
	Median	1.572	1.25	9.56	9.97	18.01	335	480
B: 200-mg High-Fat Meal	Mean	1.549	2.33	10.41	10.89	16.79	316	464
	%CV	19	40	17	17	22	21	36
	Median	1.613	2.00	10.67	11.30	17.38	295	429
C: 200-mg Low-Fat Meal	Mean	1.672	1.86	10.06	10.54	16.31	322	457
	%CV	22	26	15	14	18	14	25
	Median	1.579	1.74	9.89	10.43	16.63	320	473

Source: Section 15; Table 5 in GS-US-162-0101 Study Report

The statistical results comparing the FTC values following administration of each treatment are presented in the table below:

Statistical Analysis of FTC Oral Solution PK Parameter Estimates by Treatment

Statistic	Treatment			Statistic	Treatment Comparison	
	A	B	C		B vs. A	C vs. A
$AUC_{0\text{-}inf}$ (µg·h/mL)						
Geo LS Mean	10.20	10.73	10.44	**Geo LS Mean Ratio**	1.052	1.024
				90% CI (Lower)	1.007	0.980
				90% CI (Upper)	1.099	1.070
$AUC_{0\text{-}last}$ (µg·h/mL)						
Geo LS Mean	9.53	10.23	9.96	**Geo LS Mean Ratio**	1.073	1.044
				90% CI (Lower)	1.021	0.993
				90% CI (Upper)	1.128	1.098
C_{max} (µg/mL)						
Geo LS Mean	1.571	1.517	1.636	**Geo LS Mean Ratio**	0.966	1.042
				90% CI (Lower)	0.898	0.969
				90% CI (Upper)	1.039	1.121
t_{max} (h)						
LS Mean	1.21	2.33	1.86	**LS Mean Ratio**	1.931	1.541
				90% CI (Lower)	1.637	1.247
				90% CI (Upper)	2.225	1.835

Source: Section 15; Table 7 GS-US-162-0101 Study Report

Discussion

Based on the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} values, the 90% CI of the test/reference (solution with a high-fat meal/solution fasted) ratios of geometric least-squares means were approximately 101 to 110%, 102 to 113%, and 90 to 104%, respectively. Based on the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} values, the 90% CI of the test/reference (solution with a low-fat meal/solution fasted) ratios of geometric least-squares means were approximately 98 to 107%, 99 to 110%, and 97 to 112%, respectively. These CI are

within the 80-125% interval used to define for lack of difference between treatments; therefore, FTC oral solution can be administered with or without a high-fat meal or a low-fat meal and there will be no clinically significant affect to the FTC plasma concentrations.

Mean t_{max} values for the solution administered with a high-fat and low-fat meal were 1.1 and 0.7 hours later compared to the solution administered in a fasted state. These decreases or delays in absorption rate are not of clinical significance.

Conclusion
The administration of FTC oral solution with food has no effect on the C_{max} or the AUCs of FTC, but appeared to delay the time to maximum concentration of FTC. This delay in t_{max} would not be considered to be of any clinical significance.

4.1.3 Single-Dose PK Study

Title
FTC-105: An Evaluation of the Safety and Pharmacokinetics of Single, Escalating Oral Doses of Emtricitabine in HIV-1 Infected or Exposed Pediatric Patients Aged < 18 Years Old

Study Rationale
In adults, FTC demonstrates linear kinetics and steady-state C_{max} and AUC are predictable based on single-dose data. Therefore, a single-dose PK study of FTC administered to pediatric patients was conducted to facilitate dose selection for children of varying ages that would be furthered evaluated in Phase II and Phase III safety and efficacy studies.

Study Objectives
Primary-

- To determine the safety/tolerability of two single, escalating doses of FTC administered orally to HIV-1 infected or potentially infected pediatric subjects from birth to late adolescence (< 18 years old).
- To evaluate the PK profiles and dose proportionality of FTC following oral administration of two single, escalating doses in HIV-1 infected or potentially infected pediatric subjects.
- To determine if age-related differences exist in the safety/tolerability and PK profiles of single, oral doses of FTC in HIV-infected or potentially infected pediatric subjects.
- To determine a dosage regimen or regimens for FTC in HIV-1 infected pediatric subjects that provide plasma FTC exposures comparable to FTC exposures in adults when given a 200-mg QD dose, to be used in future Phase II/III trials evaluating the safety and efficacy of FTC in combination with other antiretroviral drugs in pediatric subjects and to provide dosing guidance in the product label.

Study Design
This was a Phase I, open-label, non-randomized, parallel-group study to evaluate the safety/tolerability and PK of single doses of FTC at two dose levels (60-mg/m^2 and 120-mg/m^2) in HIV-1 infected pediatric subjects aged < 18 years old. The original study design included 5 different Cohorts based on their age at enrollment. However, it was difficult to enroll Cohort 1 (from birth to < 3 months); therefore, this study only enrolled children into Cohorts 2, 3, 4, and 5 (ages for each Cohort defined below). An ongoing study (FTC-116) is currently evaluating FTC in pediatric patients from birth to < 3 months.

Cohort 2: 3 months old - < 2 years old
Cohort 3: 2 years old - < 6 years old
Cohort 4: 6 years old - < 13 years old
Cohort 5: 13 years old - < 18 years old

In the first two dosing periods, all subjects received single oral doses of FTC administered at two dose levels (60-mg/m^2 or 120-mg/m^2) using an oral solution formulation containing 10-mg/mL FTC. Comparison of the children's plasma profiles following single-dose administration to adult historical exposures was used to guide the selection of an FTC dose to be administered to pediatric patients in longer term trials. In a third dose period, older children (≥ 6 years old) who were capable of swallowing capsules received a third dose of FTC administered as 25-mg or 100-mg capsules. A comparison of exposures achieved with the FTC oral solution to the exposures achieved with the capsules was done to assess the preliminary relative bioavailability (BA) of the capsule formulation relative to the solution formulation.

Reviewer Note: *Although the relative BA of the capsule to the oral solution was evaluated in the third period of FTC-105, a formal relative and absolute BA study was conducted (FTC-110 in healthy volunteers). Study FTC-110 concluded the relative BA of the 200-mg FTC capsule formulation to the oral solution formulation is 124%. In FTC-110, the 200-mg FTC capsule was administered (the current marketed solid formulation of FTC) and the FTC oral solution that was administered (Formulation C-1) is the current FTC 'to-be' marketed oral solution formulation. In FTC-105, the 25-mg and 100-mg capsules were administered* (b) (4) *and the FTC oral solution (Formulation C) that was administered has been revised (Formulation C-1) and will not be marketed. Therefore, the quantitative PK results from the preliminary relative BA portion conducted in FTC-105 will be reported in the study results but not discussed.*

Study Population and Demographics
Twenty-five children were enrolled into FTC-105. Initially six study centers (three in NY and one site each in FL, TN, and SC) were initiated to conduct this study. Four of the six centers recruited the 23 children in Cohorts 3 to 5. Because of the difficulties involved in recruiting children < 2 years of age, and despite initiating an additional 5 study centers, only six children had been identified and screened for Cohort 2. Of these six children, only two were subsequently enrolled into Cohort 2. Table 1 summarizes the demographic and baseline characteristics data of patients in each cohort.

Table 1. Summary of Subject Demographics and Baseline Characteristics by Cohort

Demo/Baseline Characteristics	Cohort 2 (N=2)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=7)
Gender (n, %)				
Female	0 (0)	5 (63)	4 (50)	4 (57)
Male	2 (100)	3 (38)	4 (50)	3 (43)
Ethnicity (n, %)				
Black	2 (100)	7 (88)	7 (88)	4 (57)
Caucasian	0 (0)	0 (0)	1 (13)	0 (0)
Hispanic	0 (0)	1 (13)	0 (0)	3 (43)
Age (years)				
Median	1.9	4.1	8.7	15.4
Min, Max	1.8, 1.9	2.3, 5.7	6.6, 10.7	13.0, 17.8
Weight (kg)				
Median	13.2	15.0	30.5	57.9
Min, Max	12.4, 13.9	10.2, 24.5	21.5, 43.8	35.4, 76.0
BSA (m^2)				
Median	0.56	0.65	1.06	1.58
Min, Max	0.53, 0.59	0.48, 0.89	0.84, 138.0	1.21, 1.86
Est. CL_{cr} (mL/min)				
Median	74	75	126	177
Min, Max	60, 89	41, 165	64, 236	104, 447
Est. CL_{cr} (mL/min/1.73 m^2)				
Median	227	200	199	199
Min, Max	194, 261	145, 392	120, 429	149, 416
$CD4^+$ Cells (cells/mm_3)				
Median	1636	904	578	380
Min, Max	1103, 2169	218, 1479	211, 1153	20, 956
HIV RNA (log10 copies/mL)				
Median	3.8	4.1	2.9	4.6
Min, Max	3.3, 4.3	< 2.6, 5.3	< 2.6, 4.3	< 2.6, 5.4

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

Table 2. FTC Formulations Administered

Formulation	Theoretical Batch Size	Manufacturer's Lot #	Expiration Date
25-mg FTC Capsule	(b) (4)	TP-0006/96/AA (29029)	January 2000
100-mg FTC Capsule		TP-0006/96/ZZ	August 2000
100-mg FTC Capsule		TP-000600074 (63-338-AR)	April 2002
10-mg/mL FTC Oral Solution Formulation C		TP-0006/96/WW (980029)	December 1999

Source: Appendix 6

PK Evaluation (Plasma and Urine)

Plasma

Plasma samples to determine the FTC plasma concentrations were obtained at pre-dose and then at 0.5, 1, 2, 4, 8, 12, 24, and 48-hour post-dose.

Urine

Urine samples (where feasible considering the age of the child) were to be collected at pre-dose (single void) and over the following intervals: 0-6 and 6-12 hours following each dose of FTC. An optional urine collection was made over the following collection interval: 12-24 hours post-dose.

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

- PK parameters calculated for FTC from plasma concentration data included the following: C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, λ_z, t½, CL/F, V_z/F, and %Extrapolated AUC.
- Urinary excretion data were analyzed to determine the amount of FTC excreted (A_e) and the % of dose excreted as FTC in urine over a 24-hour post-dose interval.

Statistical Analysis

- Statistical analysis of the dose proportionality of plasma PK parameter (primarily C_{max} and AUC) values obtained following administration of 60-mg/m^2 and 120-mg/m^2 doses of FTC using the oral solution was performed.
- The primary assessment of dose proportionality was performed using a power model: $y = e^a \times dose^b$ where y is the value of PK parameter (e.g., C_{max} or AUC).
- Dose proportionality is concluded if the 90% CI of the slope from the power model is within 30% (a pre-specified acceptance range) around unity.
- A secondary analysis of dose proportionality was performed using ANOVA (SAS® Version 8.1 PROC MIXED) to compare the 60 and 120-mg/m^2 doses.

Assay/Bioanalytical Method
A validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) bioanalytical method was used to determine FTC concentrations in plasma and urine. (b) (4) , validated the method.

Plasma
Plasma samples were analyzed with calibration standards at 10 concentrations and QC samples at 4 concentrations. The precision and accuracy in the assay validation were evaluated using three analytical runs, each containing quality control (QC) samples (n=4) in replicates of five. Correlation coefficients were all greater than 0.99. Inter-day precision, expressed as %CV, ranged from 4.89 to 10.69% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from 0.0% to 5.2% for the human plasma assay.

Urine
Urine samples were analyzed in three analytical runs with calibration standards at 6 concentrations and QC samples (n=4) in replicates of five. Correlation coefficients were all greater than 0.99. Inter-day precision expressed as %CV, ranged from 5.22% to 9.67% for the human urine assay. Inter-day accuracy, expressed as %bias, ranged from -4.0% to 3.3% for the urine assay.

FTC-105 Study Results
PK Results
Individual estimates and descriptive statistics of FTC PK parameters following administration of 60 mg/m^2 and 120 mg/m^2 doses administered as the FTC oral solution (Periods 1 and 2) and the FTC capsule formulation (Period 3, Cohorts 4 and 5) are summarized in Table 3 below.

Table 3. Summary of FTC PK Parameter Estimates Following the Administration of a Single Oral Dose of FTC Oral Solution (10-mg/mL) at 60-mg/m^2 (Period 1) and 120-mg/m^2 (Period 2), Plus a Single Oral Dose of FTC Solid Capsule at 120-mg/m^2 (Period 3, Cohorts 4 and 5).

Period & Dose	Cohort Age	Statistic	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-t} (µg·h/mL)	AUC_{0-inf} (µg·h/mL	λ_z (h)	t½ (h)	CL/F mL/min	V_z/F (L)
Period 1 60-mg/m^2 Solution	2* 3-23 mos N=2	Mean	1.02	1.54	4.63	4.81	0.108	6.43	137	77
		%CV	NA	NA	NA	NA	NA	NA	NA	NA
		Median	1.02	1.54	4.63	4.81	0.108	6.43	137	77
	3 2-5 yr N=8	Mean	1.13	1.17	4.19	4.32	0.078	9.51	174	135
		%CV	32	52	27	26	28	27	46	36
		Median	1.14	1.04	4.05	4.23	0.073	9.60	171	123
	2 + 3 3 mos - 5 yr N=10	Mean	1.11	1.24	4.28	4.42	0.084	8.89	167	124
		%CV	37	48	29	28	28	29	45	42
		Median	1.14	1.08	4.05	4.23	0.080	8.70	171	103
	4 6 -12 yr N=8	Mean	1.06	0.96	4.27	4.45	0.071	10.37	254	230
		%CV	32	69	30	28	26	27	22	38
		Median	1.20	0.58	3.97	4.40	0.071	9.88	275	205
	5 12-17 yr N=7	Mean	0.89	1.61	4.01	4.15	0.090	9.29	392	307
		%CV	30	31	17	18	56	38	23	42
		Median	0.86	1.98	3.87	4.02	0.063	11.02	418	293
Period 2 120-mg/m^2 Solution	2* 3-23 mos N=2	Mean	1.513	1.52	7.84	8.13	0.059	11.93	140	145
		%CV	NA	NA	NA	NA	NA	NA	NA	NA
		Median	1.51	1.52	7.84	8.13	0.059	11.93	140	145
	3 2-5 yr N=8	Mean	1.99	1.20	7.54	7.70	0.077	9.65	196	157
		%CV	24	45	28	28	31	28	43	44
		Median	1.98	1.04	7.20	7.36	0.071	9.83	195	150
	2 + 3 3 mos - 5 yr N=10	Mean	1.90	1.26	7.60	7.79	0.074	10.11	185	155
		%CV	26	43	25	25	30	26	42	40
		Median	1.90	1.06	7.75	7.99	0.068	10.23	160	145
	4 6 -12 yr N=8	Mean	1.91	1.54	7.78	8.02	0.061	11.70	288	292
		%CV	43	73	33	31	20	20	26	29
		Median	1.95	1.08	7.63	8.04	0.059	11.80	307	307
	5 12-17 yr N=7	Mean	1.55	1.58	8.23	8.45	0.065	11.08	406	400
		%CV	17	33	41	40	18	20	37	45
		Median	1.59	1.64	7.47	7.68	0.067	10.41	401	390
Period 3 120-mg/m^2 Capsule	4 6 -12 yr N=6	Mean	2.49	1.85	10.72	10.93	0.078	10.17	213	184
		%CV	35	23	33	32	46	34	28	43
		Median	2.31	2.00	9.60	9.72	0.070	10.05	199	151
	5 12-17 yr N=6	Mean	2.15	1.32	9.20	9.38	0.065	10.77	361	341
		%CV	24	38	32	32	9	8	39	40
		Median	2.22	1.00	9.20	9.33	0.064	10.88	352	350

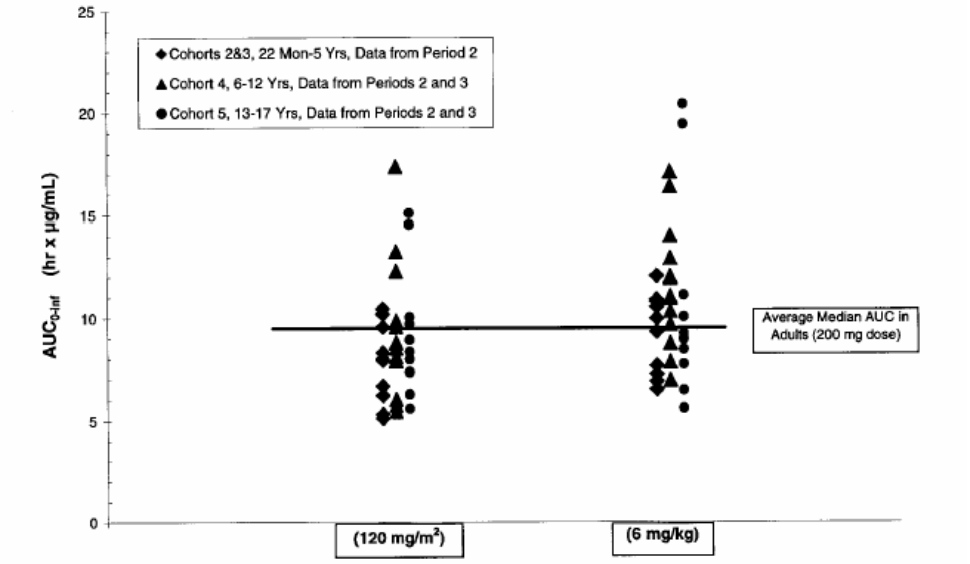
*Cohort 2: Using USP Sterile H_2O for Injection and the contents of one FTC 100-mg capsule (10-mg/mL, unflavored) a pharmacist prepared and administered to the two subjects in this Cohort and not the FTC Oral Solution because by the time the subjects were enrolled, Formulation C oral solution (b) (4) The revised oral solution (Formulation C-1) (b) (4)

FTC is rapidly absorbed as indicated by peak plasma concentrations occurring between a single 200-mg FTC dose to adults, median FTC AUC_{0-inf} and C_{max} values were 9.6 µg·h/mL and 1.8 µg/mL, respectively. The median pediatric FTC AUC_{0-inf} and C_{max} values ranged from 7.2 to 8.23 µg·h/mL and 1.51 to 1.98 µg/mL for the 120-mg/m^2

solution dose (all Cohorts) and 9.20 to 9.60 µg·h/mL and 2.22 to 2.31µg/mL in the capsule groups (Cohorts 4 & 5), respectively. These pediatric exposure values are slightly lower than the reported adult exposure values. The lowest pediatric exposure values reported for the 120-mg/m^2 dose level was for the FTC oral solution. This is not unexpected, since in FTC-110 (the relative and absolute BA study) it was reported the FTC solution formulation achieved about 24% lower FTC exposures relative to the capsule formulation. These slightly lower values seen in the pediatric subjects are most likely due to the BA difference.

After the results for FTC-105 were analyzed, the applicant selected 120-mg/m^2 to 140-mg/m^2 as the pediatric dose for FTC that would achieve similar plasma exposure as reported in adults given 200-mg daily. However, DAVDP recommended the Sponsor pursue a mg/kg dose, rather than a mg/m^2 dose. Based on the $AUC_{0\text{-inf}}$ values in children in FTC-105 following the 120-mg/m^2 dose (oral solution) and the body weight data, a dose of 6-mg/kg (up to a maximum of 200-mg daily) was selected as the FTC dose for subsequent long term safety and efficacy trials in pediatric subjects. Figure 1 below illustrates the projected $AUC_{0\text{-inf}}$ values for each age group of children if administered a 6-mg/kg (up to a maximum 200-mg a day) FTC dose. The projected $AUC_{0\text{-inf}}$ values are similar to or slightly higher than the $AUC_{0\text{-inf}}$ values achieved in FTC-105 after administering the 120-mg/m^2 oral solution dose. Figure 1 indicates at least 50% of children who receive FTC at the 6-mg/kg dose will have AUC values above the median AUC value (9.6 µg·h/mL) reported in adults receiving the 200-mg dose.

Figure 1. Plots of FTC $AUC_{0\text{-inf}}$ at 120-mg/m^2 and 6-mg/kg Doses by Age Cohort



Mean CL/F values in this study increased with increasing age; however, these differences were greatly minimized once the CL/F values were normalized for body weight or body surface area (BSA) shown in Table 4 below.

Table 4. Normalized Apparent Total Body Clearance and Apparent Volume of Distribution Values for FTC Following Single Oral Doses of 60 and 120-mg/m^2 in the Solution Formulation

	Statistic	60-mg/m$_2$ Dose			120-mg/m^2 Dose		
		CL/F/kg mL/min/kg	CL/F mL/min/1.73m^2	V_z/F L/kg	CL/F/kg mL/min/kg	CL/F mL/min/1.73m^2	V_z/F L/kg
2 3-23 mos N=2	Mean	9.54	401	5.34	10.37	426	10.73
	%CV	44	46	47	5	3	14
	Median	9.54	401	5.34	10.37	426	10.73
3 2-5 yr N=8	Mean	10.39	434	8.28	11.62	484	9.51
	%CV	34	36	33	24	29	30
	Median	8.80	409	7.36	11.27	476	9.47
2 + 3 3 mos 5 yr N=10	Mean	10.22	427	7.69	11.37	472	9.75
	%CV	34	36	37	22	26	26
	Median	8.80	409	7.17	10.37	433	10.50
4 6 -12 yr N=8	Mean	8.53	417	7.41	9.43	465	9.65
	%CV	35	28	33	31	27	39
	Median	7.28	395	7.50	8.54	431	9.03
5 12-17 yr N=7	Mean	6.89	427	5.40	7.17	442	7.05
	%CV	13	16	37	21	27	36
	Median	6.79	430	5.89	7.32	453	6.77

Statistical Analysis of PK Data of FTC

The results of the statistical analysis of FTC PK parameter estimates between the two solution doses (60 and 120-mg/m^2) using the power model analysis and ANOVA demonstrated that C_{max} and AUC values for FTC are dose proportional between 60 and 120-mg/m^2 doses across all age cohorts. Figures 2 and 3 below depict the linearity and dose proportionality in the PK parameters ($AUC_{0\text{-inf}}$ and C_{max} values). The power model analysis showed that the 90% CI for the slope contained 1.0 for each parameter analyzed and the ANOVA showed that the 90% CI for the dose normalized C_{max} and AUC values were all within the range for either 20% or 30% difference around unity.

Figure 2. Plots of Mean FTC $AUC_{0\text{-inf}}$ vs. Dose in Solution by Age Cohort

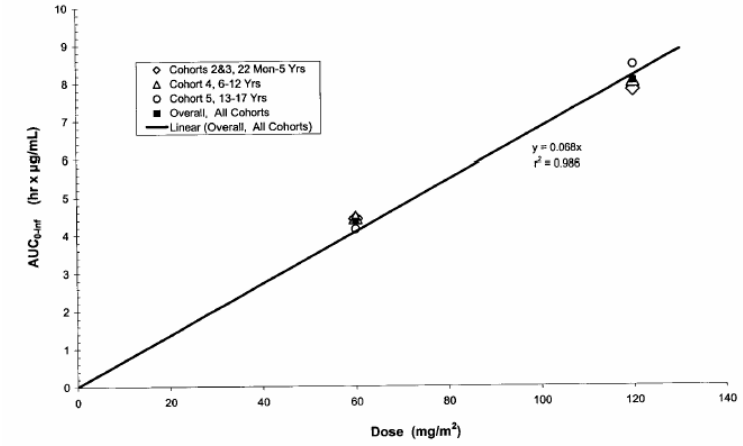
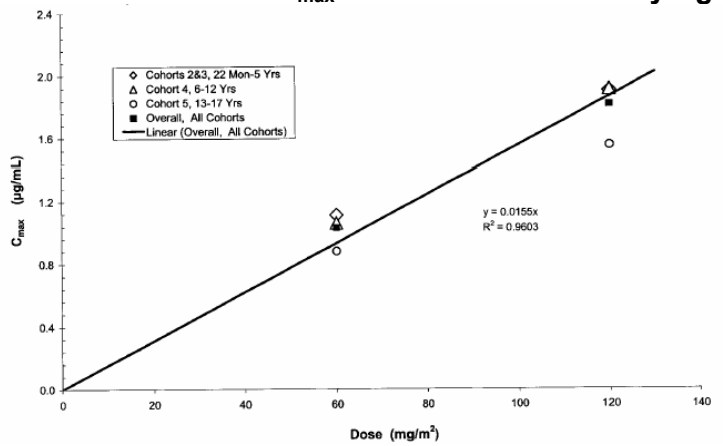


Figure 3. Plots of Mean FTC C_{max} vs. Dose in Solution by Age Cohort



Urinary Excretion Data of FTC

Over the urine collection period of 24-hours post-dose, approximately 35-60% of the FTC oral dose was recovered in urine (unchanged FTC). Past experience with adult urine collection demonstrated that a 48-hour post-dose collection is necessary to have complete urinary recovery of unchanged FTC (approximately 60 to 70% of an oral dose). No differences in the percentage of FTC dose recovered in urine between age cohorts following the solution or capsule administration were seen. Not surprising, the renal clearance values unadjusted for body surface area increased with increasing age. Once renal clearance was adjusted for BSA, the differences in renal clearance between age cohorts was minimized.

As seen in adult observations (FTC-107), there was almost a linear increase in CL/F values as CL_{cr} increased, as shown in Figure 4 below. Results from a linear regression analysis of FTC CL/F values in children during Dose Periods 2 and 3 vs. CL_{cr} values are depicted in Figure 5. There is a statistically significant linear relationship between the CL/F of FTC and CL_{cr} as described by the equation of:

$CL/F = (-21.92) + 2.14 \times CL_R$, with $r^2=0.681$

Figure 4. Plots of FTC CL/F (Apparent Total Body Clearance) vs. CL_{cr} (Estimated Creatinine Clearance) (Dose Periods 2 & 3)

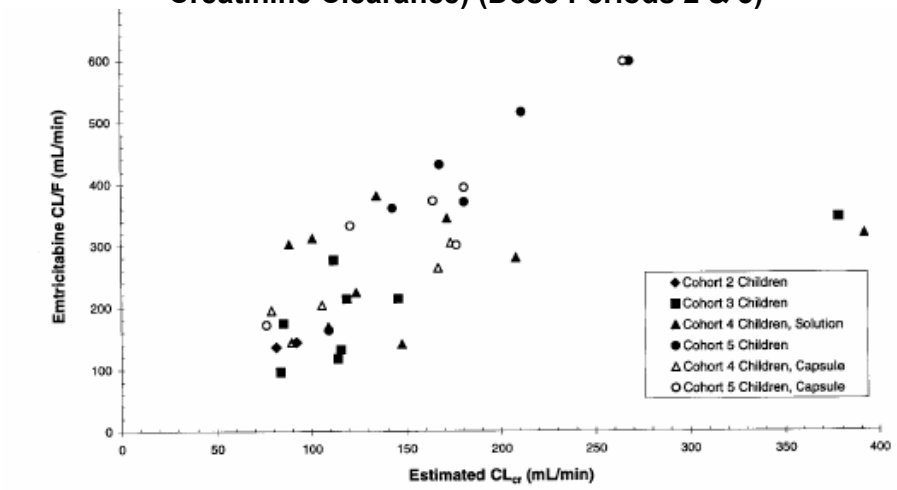
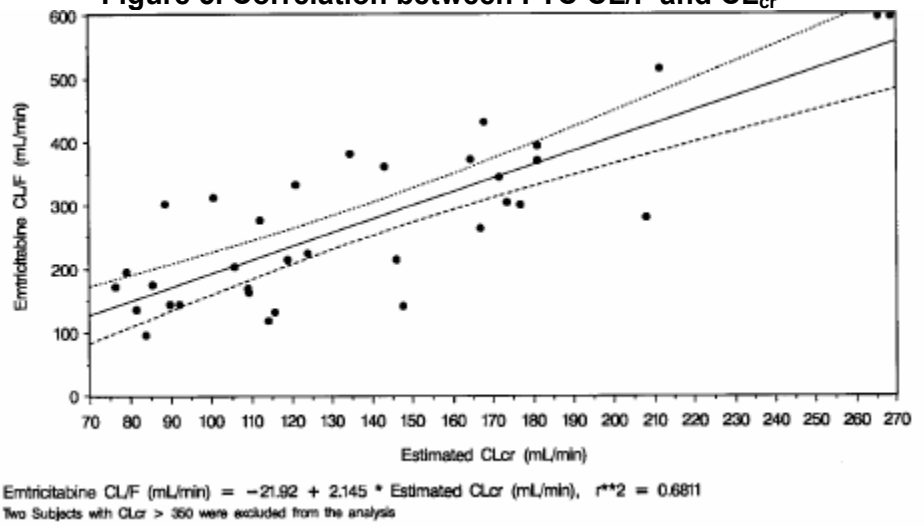


Figure 5. Correlation between FTC CL/F and CL_{cr}



Assessment/Conclusion

FTC oral solution and capsule were rapidly absorbed in children, similar to findings seen in adults. The median pediatric FTC $AUC_{0\text{-}inf}$ and C_{max} values ranged from 7.2 to 8.23 µg·h/mL and 1.51 to 1.98 µg/mL for the 120-mg/m^2 solution dose (all Cohorts) and 9.20 to 9.60 µg·h/mL and 2.22 to 2.31µg/mL in the capsule groups (Cohorts 4 & 5), respectively. These pediatric exposure values are slightly lower than the reported adult exposure values after administering a single 200-mg daily dose (adult median $AUC_{0\text{-}inf}$ and C_{max} values were 9.6 µg·h/mL and 1.8 µg/mL).

After analyzing the PK data from the 120-mg/m^2 solution dose and considering the body weight of the enrolled children in FTC-105, the applicant selected 6-mg/kg QD (up to a 200-mg maximum) as the dose to take forward into Phase II and III longer term trials. Projected exposures (AUC) for this dose are similar to adult AUC values when administered a 200-mg daily dose. At least 50% of the projected AUC values for the 6-mg/kg FTC pediatric dose are above the reported median AUC adult value of 9.6 µg·h/mL.

Mean CL/F values in this study increased with increasing age; however, these differences were greatly minimized once the CL/F values were normalized for body weight or BSA. As seen in adults (FTC-107), there was almost a linear increase in CL/F values as CL_{cr} increased. There is a statistically significant linear relationship between the CL/F of FTC and CL_{cr} as described by the equation of:
$CL/F = (-21.92) + 2.14 \times CL_R$, with $r^2=0.681$.

The FTC PK parameter estimates for the two solution doses (60 and 120-mg/m^2) were analyzed using the power model and ANOVA. Results demonstrated that C_{max} and AUC values for FTC are dose proportional between 60 and 120-mg/m^2 doses across all age cohorts.

Reviewer Note: *The selected pediatric dose of 6-mg/kg (up to a maximum of 200-mg QD) is an appropriate dose to be administered in the subsequent Phase II and III safety and efficacy trials. It appears, even with the BA difference of the solution compared to*

the capsule (solution approximately 24% less BA than capsule), the 6-mg/kg dose should achieve FTC plasma levels in pediatric patients similar to the reported adults plasma levels.

The youngest child enrolled in this study was 22 months old. No data exists for children > 3 months to < 22 months. Subjects within this age bracket were enrolled into FTC-203 and FTC-202. Therefore; PK data for younger children will be reported the study reports for FTC-203 and FTC-202.

4.1.4 Phase II Safety, PK, and Antiviral Activity Studies

Title
Combined Analysis of Three Phase II Safety, Antiviral Activity, and Pharmacokinetic Studies Conducted in Pediatric Patients (FTC-203, FTC-202 [PACTG1021], and FTC-211).

Study Rationale
A previous single-dose pediatric pharmacokinetic (PK) study (FTC-105) identified a pediatric dose of FTC (6-mg/kg QD, up to a maximum of 200-mg QD) to take forward into long term Phase II safety and PK trials. Three Phase II pediatric safety and PK trials were conducted (FTC-203, FTC-202 (PACTG1021), and FTC-211). FTC-211 is complete; however, FTC-203 and FTC-202 are currently ongoing (> 96 weeks of safety data has been collected to date). A combined analysis of the 77 HIV-infected pediatric subjects ranging from 3 months to 17 years of age who had PK data collected between Week 2 and Week 4 while enrolled will be provided in this review. The results from FTC-105 and these three Phase II safety and PK studies provide adequate data to establish FTC dosing guidelines for pediatric patients (3 months to 17 years of age).

Study Titles
FTC-203: An Open-Label Study of a Once Daily Dose of FTC in Combination with Other Antiretroviral Agents in HIV-Infected Pediatric Subjects.

FTC-202: An Open-Label Study to Evaluate the Safety, Tolerance, Antiviral Activity and Pharmacokinetics of FTC in Combination with Efavirenz and Didanosine in a Once Daily Regimen in HIV-Infected Antiretroviral Therapy Naïve or Very Limited Antiretroviral Exposed Pediatric Subjects (PACTG1021).

FTC-211: An Open-Label Study of a Once-Daily Dose of FTC in Combination with Other Antiretroviral Agents in HIV-Infected Pediatric Subjects.

Objectives for All 3 Studies
- To obtain safety experience for antiretroviral regimens containing FTC in HIV-1 infected pediatric patients.
- To determine the steady-state FTC concentrations in HIV-1 infected pediatric subjects and, if necessary, to refine the dose of FTC to achieve plasma concentrations comparable to those in adults given 200-mg FTC once daily.
- To obtain antiretroviral activity data for antiretroviral regimens containing FTC in HIV-1 infected pediatric patients.

Study Designs

FTC-203

This is an ongoing multi-center, open-label, non-randomized Phase II clinical study designed to evaluate the safety, antiretroviral activity, and PK of FTC in combination with other antiretroviral agents. The study was designed to enroll approximately 60 to 120 HIV-1 infected antiretroviral naïve and experienced pediatric subjects between the ages of 3 months and 17 years of age, separated in the following age groups (N=PK subjects):

- Group 1: 3 months to 24 months (N=14)
- Group 2: from 25 months to 6 years of age (N=9)
- Group 3: from 7 years to 12 years of age (N=9)
- Group 4: from 13 years to 17 years of age (N=3)

- Naïve subjects received 6-mg/kg FTC (up to a maximum of 200-mg QD for the capsule and up to a maximum of 240-mg QD when using the oral solution) + stavudine (d4T) (1-mg/kg BID if < 30-kg, 30-mg BID if 30 to 59 kg; 40-mg BID if $\geq$ 60 kg) + lopinavir/ritonavir (LPV/RTV) (12/3-mg/kg BID if $\geq$ 7 to < 15 kg; 10/2.5 mg/kg BID if $\geq$ 15 to $\leq$ 40 kg; 400/100 mg if > 40 kg).
- Experienced subjects: Replaced their 3TC in their existing antiretroviral regimens with FTC (up to a maximum of 200-mg QD for the capsule and up to a maximum of 240-mg QD when using the oral solution). At the investigator's discretion, one or more of the subject's background medications could be replaced at the same time 3TC was replaced.

FTC-202 (PACTG1021)

This is an ongoing open-label, non-randomized trial designed to evaluate the safety, tolerance, antiviral activity, and PK of FTC when combined with efavirenz (EFV) and didanosine (ddI) in a fully once daily regimen in HIV-infected antiretroviral therapy naïve or very limited antiretroviral exposed pediatric subjects. Enrollment in the two oldest age groups (N=37) was completed in October 2002, which included (N=PK subjects):

- Group 2: from 3 years to 12 years of age (N=17)
- Group 3: from 13 years to 21 years of age (N=14)

Reviewer Note: Subjects who were > 17 years of age were not included in the combined PK analysis. Additionally, Group 1 (N=16) will start enrolling subjects once the EFV dose has been established for subjects from 3 months to < 3 years of age.

All subjects received a triple drug regimen comprised of:

- FTC 6-mg/kg QD up to a maximum of 200mg QD (regardless of formulation administered) + ddI 240-mg/m^2 QD (up to a maximum of 400-mg QD) + EFV (based on body weight up to a maximum of 600-mg QD as a capsule or up to 720-mg QD as an oral solution).

FTC-211

This was an open-label, non-randomized clinical study designed to evaluate the safety, PK, and antiretroviral activity of FTC containing regimens in naïve and experienced HIV-1 infected pediatric subjects. Depending on their age, HIV-1 infected pediatric subjects < 18 years of age were to receive one of two FTC containing regimens. Sixteen subjects were enrolled into the following age groups (N=PK subjects):

Group 2: 7 to 12 years of age (N=1)
Group 3: 13 to 17 years of age (N=15)

- Naïve and experienced patients received FTC (up to a maximum of 200-mg QD for the capsule and up to a maximum of 240-mg QD when using the oral solution) + ddI (240-mg/m^2 up to a maximum of 400-mg daily) + EFV (based on body weight up to a maximum of 600-mg QD as a capsule or up to 720-mg QD as an oral solution).

Combined Studies Populations and Demographics
The subjects in the combined PK analysis include all the subjects for whom reliable PK data were available. Four subjects in FTC-202 were > 18 years of age and were not included in the analysis. In addition, subject #0104 in FTC-203 was not included in the overall analysis as the mean AUC_{tau} for this subject was 1.99 µg·h/mL, approximately 4-fold less than mean and median values in the age group. This subject was identified as having a high non-adherence of drug administration, documented on several study visits by the amount of medication the subject would have remaining in the bottle dispensed two weeks prior. Table 1 below summarizes the demographics of the subjects included in this combined analysis.

Table 1. Summary Demographic and Dosing Information by Age Group (3 months to 18 years) for Subjects Receiving FTC Capsules and Solution in Pediatric Clinical Studies

Characteristics	1 (3 to 24 mo) (N 15)[c]	2 (25 mo to 6 yr) (N 19)	3 (7 to 12 yr) (N 17)	4 (13 to 17 yr) (N 27)
Formulation				
Capsule	0	0	10	26
Oral Solution	15	19	7	1
Race (N)				
Black	14	4	9	11
White	0	2	1	15
Hispanic	0	6	1	1
Other	1	7	6	0
Gender				
Male	8	10	7	11
Female	7	9	10	16
Age (yr)[a]	1.4 (0.4–2.1)	5.0 (3.0–6.8)	10.0 (7.1–12.8)	15.2 (13.2–17.9)
Weight (kg)[b]	9.4 (4.8–13.4)	18.5 (13.0–26.4)	32.5 (19.1–64.5)	51.3 (23.0–111)
BSA (m^2)[b]	0.44 (0.28–0.58)	0.73 (0.58–0.91)	1.09 (0.75–1.64)	1.487 (0.90–2.33)
Dose (mg/kg)[a]	6.1 (5.5–6.8)	6.1 (5.6–6.7)	5.6 (3.1–6.6)	4.4 (1.8–7.0)

a Mean (range) age on day of pharmacokinetic evaluation
b Mean (range)
c Includes subject 0104 (study FTC-203) who was excluded from the pharmacokinetic analysis
Source: Appendix 2.7.2.5, Table 2.7.2.5

Table 2. FTC Formulations

Study Drug	Study	Lot #	Manufacturer Lot #	Expiration Date
200-mg Capsule	FTC-203	TP-0006-01031 TP-0006-00133 TP-0006-00205 W302A1	75-042-4Q 66-382-AR 70-035-4Q 96-074-4Q-21	May 2004 September 2004 December 2004 January 2005
10-mg/mL Oral Solution	FTC-203	TP-0006-00175 TP-0006-00211 TP-0006-00216 TP-0006-01015 TP-0006-03003	68-002-4P 72-010-4T 73-011-4T 74-012-4T 96-017-4T	September 2001 February 2005 February 2005 April 2005 January 2005
200-mg Capsule	FTC-211	TP-0006-02017 TP-000601030	85-060-4Q 73-041-4Q	February 29, 2004 March 31, 2005
10-mg/mL Oral Solution	FTC-211	TP-0006-00216	73-011-4T	February 28, 2005
200-mg Capsule	FTC-202	TP-0006-00205 TP-0006-01109 W302A1 W304A1 W401A1	70-035-4Q 78-045-4Q 96-074-4Q-21 07-081-4Q-22 15-087-4Q-21	December 2004 October 2004 January 2005 August 2006 May 2007
10-mg/mL Oral Solution	FTC-202	TP-0006-00211 TP-0006-01015 TP-0006-03003 13582AW21 150194T21	72-010-4T 74-012-4T 96-017-4T 13582AW21 150194T21	February 2005 April 2005 January 2006 January 2006 May 2007

Reviewer Note: *The FTC-202 report provided in this submission is only a summary. The summary does not provide the Lot #'s/Expiration date of the FTC formulations administered to the study subjects*

PK Evaluation

Plasma

For all three studies, plasma samples to determine the FTC plasma concentrations were obtained at pre-dose and then at 0.5, 1, 2, 4, 8, 12, and 24-hour post-dose following each dose of FTC.

PK Analysis

Plasma FTC concentration-time data were analyzed by noncompartmental methods using WinNonlin, Professional version 3.1 (FTC-203 and FTC-211) and ADAPT II Release 4 (FTC-202 PACTG1021) .

- PK parameters calculated for FTC from plasma concentration data included the following: C_{max}, C_{min}, t_{max}, AUC_{tau}, λ_z, t½, CL/F, and V_z/F.
- PK parameters for each subject are summarized using descriptive statistics (sample size, arithmetic mean, geometric mean, SD, %CV, minimum, median, and maximum, 95% CI, mean of log, SD of log).

Assay/Bioanalytical Method

A validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) bioanalytical method was used to determine FTC concentrations in plasma and urine. (b) (4) validated the method.

FTC-203: Plasma samples were analyzed with 8 calibration standards and a minimum of 8 QC samples per analytical run. Correlation coefficients were all greater than 0.99. The precision and accuracy in the assay validation were evaluated using three analytical runs, each containing quality control (QC) samples (n=4) in replicates of five. Inter-day

precision, expressed as %CV, ranged from 3.7% to 7.2% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -2.6% to 8.2% for the human plasma assay.

FTC-211: Plasma samples were analyzed with 8 calibration standards and a minimum of 9 QC samples per analytical run. Correlation coefficients were all greater than 0.99. The precision and accuracy in the assay validation were evaluated using three analytical runs, each containing quality control (QC) samples (n=4) in replicates of five. Inter-day precision, expressed as %CV, ranged from 2.3% to 7.5% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -2.4% to 4.9% for the human plasma assay.

FTC-202 (PACTG1021): Plasma samples were analyzed with 10 calibration standards and a minimum of 8 QC samples per analytical run. Correlation coefficients were all greater than 0.99. The precision and accuracy in the assay validation were evaluated using three analytical runs, each containing quality control (QC) samples (n=4) in replicates of five. Inter-day precision, expressed as %CV, ranged from 4.90% to 10.90% for the human plasma assay. Inter-day accuracy, expressed as %bias, ranged from -1.0% to 7.2% for the human plasma assay.

Combined Analysis Study Results (FTC-203, FTC-202, FTC-211)
PK Results
The subjects in the combined PK analysis include all subjects who had reliable PK data available. Four subjects enrolled into FTC-202 were > 18 years of age and were excluded from this analysis. FTC PK parameter estimates are summarized in Table 3 below by age group for all subjects and Table 4 by age group for subjects who received only the oral solution formulation. Table 5 below summarizes the PK results of three steady-state studies in adults who took 200-mg FTC daily, healthy volunteers and HIV-1 infected.

Table 3. Phase 2 studies: Mean (%CV) Values for FTC PK Parameters at Steady-State by Age Group for Subjects Receiving Capsules and Solution

Age Group	N		C_{max} (μg/mL)	C_{min} (μg/mL)	t_{max} (hr)	AUC_{tau} (hr•μg/mL)	$t_{1/2}$ (hr)	CL/F (mL/min/kg)
1 3–24 mo	14[a]	Mean CV%	1.93 34	0.059 52	1.6 54	8.70 37	8.87 36	13.2 34
2 25 mo–6 yr	19	Mean CV%	1.91 38	0.059 71	1.6 62	9.03 33	11.29 57	13.0 46
3 7–12 yr	17	Mean CV%	2.72 30	0.066 45	1.7 99	12.57 28	8.19 39	8.4 54
4 13–17 yr	27	Mean CV%	2.73 31	0.064 94	1.7 65	12.55 43	8.94 37	6.4 45

[a] Subject 0104 (Study-FTC-203) was excluded from the summary statistics
Source: Appendix 2.7.2.5, Table 2.7.2.5

Table 4. Phase 2 Studies: Mean (%CV) Values for FTC PK Parameters at Steady State by Age Group for Subjects Receiving Oral Solution

Age Group	N		Cmax (µg/mL)	Cmin (µg/mL)	tmax (hr)	AUCtau (hr·µg/mL)	t1/2 (hr)	CL/F (mL/min/kg)
1 3–24 mo	14	Mean CV%	1.93 34	0.059 52	1.6 54	8.70 37	8.87 36	13.2 34
2 25 mo–6 yr	19	Mean CV%	1.91 38	0.059 71	1.6 62	9.03 33	11.29 57	13.0 46
3 7–12 yr	7	Mean CV%	2.64 37	0.057 49	1.3 38	11.01 37	8.60 35	11.21 55
4 13–17 yr	1	Mean CV%	3.84 —	0.046 —	1.0 —	14.83 —	10.59 —	7.83 —

Source: Appendix 2.7.2.5, Table 2.7.2.8

Table 5. Summary of Mean (%CV) Steady-State PK Parameter Estimates in Adults for FTC Following 200-mg Once Daily Dose

Clinical Study (Protocol) No.	Subjects Number (M/F)Type Age: mean (range)	C_{max} (µg/mL)	t_{max} (hr)	C_{min} (µg/mL)	AUC_{tau} (hr•µg/mL)	t1/2 (hr)	CL/F (mL/min)
FTC-101	8 (8M/0F) HIV-infected subjects 37 (29–42) yr	1.72 (53%)	2.00 (48%)	0.05 (24%)	8.00 (15%)	8.24 (31%)	425 (15%)
FTC-106	5 (5M/0F) Healthy volunteers 37 (33–42) yr	1.72 (16%)	1.00 (0%)	0.07 (28%)	10.04 (18%)	10.2 (19%)	339 (20%)
FTC-303	12 (1M/11F) HIV-infected subjects 38 (21–61) yr	1.94 (24%)	1.80 (58%)	0.11 (71%)	11.31 (29%)	8.08 (32%)	317 (27%)

PK Discussion

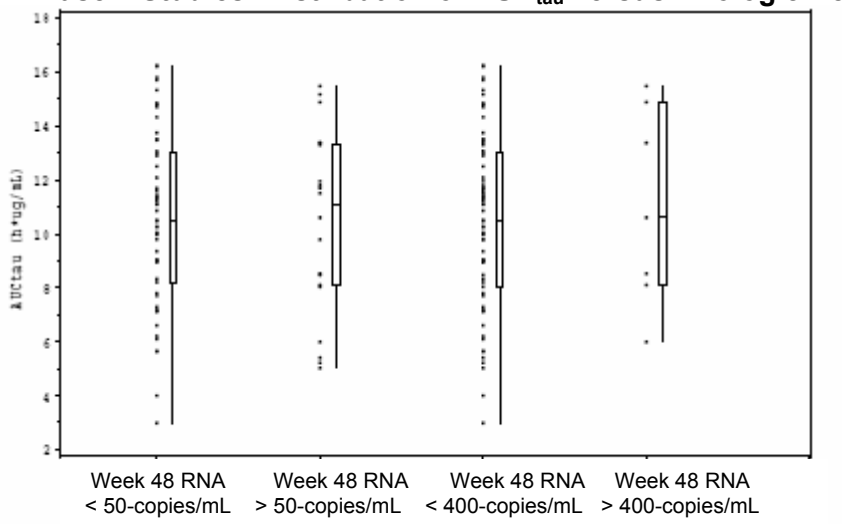
Based on the initial single-dose escalation study of FTC in HIV-infected children (FTC-105), a dose of 6-mg/kg once daily, with a maximum of 200-mg once daily, was expected to achieve a target daily AUC_{tau} of at least 6-µg·h/mL (which is the 10^{th} percentile of the adult AUC given 200-mg QD). The study protocols for FTC-203 and FTC-211 were amended to increase the maximum daily dose for subjects taking the oral solution to 240-mg daily, due to the decreased bioavailability (BA) of the solution relative to the capsule demonstrated in study FTC-110 (approximately 24% less BA for the solution).

AUC_{tau} values for 5 subjects in study FTC-203, (Subjects 105, 106, 303, 402, and 558), and 2 subjects in study FTC-202, (Subjects 669309 and 730092), were at or below this planned minimum target. The AUC_{tau} values for Subjects 105, 106, 303, 402, and 558 in study FTC-203 were 2.99, 5.22, 5.02, 5.99, and 5.64 µg·h/mL, respectively. At Week 48, the HIV-RNA viral loads of 4/5 of these subjects were $\leq$ 400 copies/mL. The HIV-RNA viral load of Subject 402 was > 400 copies/mL. The AUC_{tau} values for Subject 669309 and 730092 in study FTC-202 were 5.40 and 4.00 µg·h/mL, respectively. At the time of

data cut-off for update analysis, Subjects 660309 and 730092 had reached Weeks 15 and 35 of study FTC-202. Both subjects' viral loads were < 50-copies/mL.

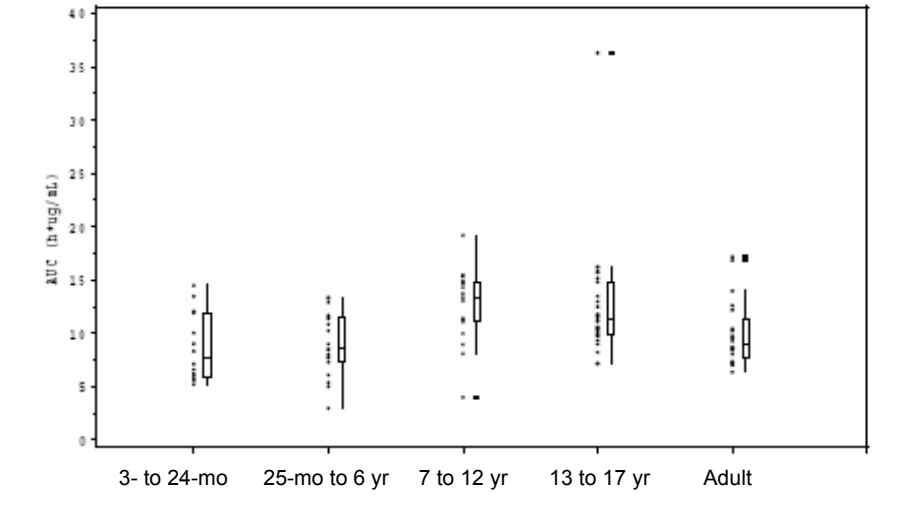
The distribution of AUC_{tau} values versus virologic response (≤ 400 copies/mL and ≤ 50 copies/mL) is presented in Figure 1 below.

Figure 1. Phase 2 Studies: Distribution of AUC_{tau} versus Virologic Response



The mean AUC_{tau} for the 20 HIV-infected adults in studies FTC-101 and FTC-303 is 10.0 µg·h/mL (CV=31%, range 6.4-17.2 µg·h/mL). The mean C_{max} was 1.85 µg/mL (CV-36%, range 0.890-3.720 µg/mL). For the pediatric Age Groups 1 and 2 (3 months to 6 years of age) the mean AUC_{tau} value was approximately 9 µg·h/mL. For children age 7 and older, the mean AUC_{tau} values were slightly higher than in adults receiving 200-mg QD (mean AUC_{tau} for subjects in Age Group 3 and 4 (7 to 18 years) was 12.5 µg·h/mL, approximately 11% higher than FTC-303, a pivotal efficacy study in adults). Although the mean AUC_{tau} values were slightly higher in older children, the values for all age groups fell within the range seen in adults. This is illustrated in Figure 2 below where the distribution of AUC_{tau} values by age group of pediatric subjects receiving FTC 6-mg/kg QD and 20 adults receiving 200-mg FTC QD are depicted.

Figure 2. Combined Analysis: Distribution of AUC (µg·h/mL) by Age Cohort



Conclusion

- Adequate number of subjects was studied to characterize the PK in children 3 months of age up to 17 years of age.
- The FTC AUC_{tau} achieved in children receiving a 6-mg/kg daily dose up to a maximum of 240-mg is similar to exposure achieved in adults receiving a dose of 200-mg daily.
- Younger children had higher variability in PK compared to adults. This may be due to a greater variability in drug clearance or perhaps due to the difficulties associated in dosing liquid formulations to young children.
- Based on the approximate 20% lower BA of the solution formulation compared to the capsule formulation, the pediatric dosing recommendation is:
    - FTC oral solution: 6-mg/kg QD up to a maximum dose of 240-mg daily
    - FCT capsule: 1 x 200-mg capsule QD for children > 33 kg and who can swallow an intact capsule.
- The proposed pediatric dose has demonstrated durable clinical efficacy and acceptable safety when combined with other antiretroviral drugs in all three Phase II studies.

4.2 OCBP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	**21-896**	**Sponsor:**	**Gilead**
IND:	53,971		
Brand Name:	EMTRIVA® Oral Solution (10-mg/mL)	**Priority Classification:**	P1
Generic Name:	Emtricitabine Oral Solution (10-mg/mL)	**Indication(s):**	Treatment of HIV-Infection
Drug Class:	NRTI	**Date of Submission:**	29March2005
Dosage Form:	Oral Solution	**Route of Admin.:**	Oral
Dosing Regimen:	Emtricitabine (6-mg/kg) QD up to 240 mg QD	**Due Date of Review:**	29September2005
Division:	DPEIII	**Medical Division:**	HFD-530
Reviewer:	J. L. DiGiacinto	**Team Leader:**	K. S. Reynolds

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies			
Mass Balance Study		X	
BA Studies			
Absolute BA [FTC-110]	X		
Relative BA [FTC-110]	X		
BE Studies			
Average BE		X	
Population BE		X	
Individual BE		X	
Food-Drug Interaction [GS-US-162-0101]	X		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)		X	
Studies Using Human Biomaterials			
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies			
PK, and Initial Safety and Tolerability in Healthy Volunteers			
Single Dose		X	

Multiple Dose		X	
PK, and Initial Safety and Tolerability in Patient Volunteers			
Single Dose [FTC-105]	X		
Multiple Dose [FTC-203, FTC-202, FTC-211]	X		
Dose Proportionality			
Single Dose		X	
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors			
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors			
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format		X	
Other			
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	
Literature References		X	

This application is√ is not___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)
Are there any outstanding issues or concerns raised in NDA 21-785 that have not been adequately addressed by the applicant? No

Requests/Comments are ___ are not ___ to be sent to firm. If any was sent, indicate the date of FDA letter.
PM Consult

1.1 Signature _____ _____

Primary Reviewer **Secondary Reviewer**

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
9/26/2005 12:02:19 PM
BIOPHARMACEUTICS

Kellie Reynolds
9/27/2005 02:55:17 PM
BIOPHARMACEUTICS