U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-896 / N 000
Drug Name:	Emtriva® (emtricitabine, 2'3'Dideoxy-5-fluoro-3'thiacytidine) 10mg/mL oral solution
Indication(s):	Treatment of HIV infection in pediatric patients
Applicant:	Gilead Sciences, Inc.
Dates:	Submitted: March 29, 2005 Received: March 30, 2005 User Fee Date: September 30, 2005
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics III (HFD-725)
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Keywords: Pediatrics, Phase II trials, Non-randomized, Pediatric AIDS Clinical Trials Group (PACTG), Time to Loss of Virologic Response (TLOVR) algorithm, Cross-sectional

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1. EXECUTIVE SUMMARY

Emtriva® (Emitricitabine) is a nucleoside reverse transcriptase inhibitor with activity against HIV-1 reverse transcriptase. It was granted traditional approval by the FDA on July 2, 2003 under NDA 21,500. The currently approved adult dose for Emtriva is 200 mg capsule QD.

Gilead Sciences, Inc. submitted the clinical study report and data on three open-label, non-randomized, single arm clinical studies FTC203, FTC-202 and FTC-211 to evaluate the safety, antiviral activity and pharmacokinetics of Emtricitabine in 169 HIV infected pediatric subjects age 3 month and older. Patients were treated with Emtricitabine in combination with other antiretroviral agents. Emtricitabine was supplied as a 200 mg capsule or as a 10 mg/mL oral solution, administered with a dose of 6 mg/kg QD using the capsule or the oral solution formulations.

The FTC-203 enrolled antiretroviral therapy (ART)-naïve and ART-experienced patients 3 months to 16 years, and studies FTC-202 and FTC-211 enrolled antiretroviral therapy naïve or very limited antiretroviral exposed patients age 3-21 years. Among them, 47% were male, 15% Caucasian, 61% Black and 24% Hispanic or other race ethnic origin.

1.1 Conclusions and Recommendations

Emitricitabine in combination with other antiretroviral agents achieved virologic suppression rates in HIV-1 infected pediatric subjects that are consistent with those of the adult studies. Since the studies were not controlled, therefore no definitive efficacy conclusion can be stated for the oral solution of Emitricitabine.

Based on analyses of the Week 48 data in three single arm clinical studies FTC203, FTC-202 and FTC-211, the overall proportions of subjects had achieved virologic suppression were 87% and 74% for <400 copies/mL and <50 copies/mL, respectively. These rates were similar between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients. The overall median change from baseline in CD4+ cell count at Week 48 was 205 cells/mm^3. Change from baseline in CD4+ cell count was statistically significantly different between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients: the ART-experienced subjects had a median CD4+ decline of 72 cells/mm^3, while the ART-naïve or very limited ART exposed pediatric patients had median CD4+ increase of 201-330 cells/mm^3.

Based on analyses of the Week 96 data in clinical study FTC203, 40.5% of the study subjects have discontinued the treatment. Most of the subjects (89.9%) remaining in the study continued their suppression of HIV-1 RNA at Week 96.

1.2 Brief Overview of Clinical Studies

The sponsor submitted data from three phase II pediatric studies FTC-203, FTC-202 and FTC-211 for efficacy evaluation. All three studies were multicenter, open-labeled, non-randomized trials of a once daily dose of Emtricitabine in combination with other antiretroviral agents to evaluate the safety, antiviral activity and pharmacokinetics of Emtricitabine (FTC) in HIV infected pediatric subjects. The FTC-202 was designed to evaluate tolerability of FTC in combination with other antiretroviral agents. The minimum treatment duration was 48 weeks.

- Studies FTC-203 and FTC-211 enrolled antiretroviral therapy (ART)-naïve and ART-experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine) patients 3 months to 17 years. The FTC-202 enrolled antiretroviral therapy naïve or very limited antiretroviral exposed patients age 3-21 years.

- The FTC-203 was conduced in 12 sited of the USA, Mexico, Panama and South Africa and the FTC-202 was conducted in the USA. The FTC-211 was a Week 48 study conducted in Romania.

- Subjects were given the option to access to emtricitabine beyond Week 96 in the FTC-203 and Week 192 in the FTC-202, providing the subjects continued to have virologic success.

- The FTC-203 and the FTC-211 are studies conducted by Gilead Science, Inc. The FTC-202 (PACTG-1021) is conducted by the Pediatric AIDS Clinical Trials Group (PACTG) and sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS) and the National Institute of Child Health and Human Development (NICHD) under a PACTG IND.

- The FTC-203 and the FTC-202 are on-going studies, while the FTC-211 has been completed.

1.3 Statistical Issues and Findings

The following are findings regarding the emtricitabine efficacy endpoints.

1. Through 48 weeks of therapy, the overall proportion of patients who achieved and sustained an HIV RNA <400 copies/mL was 87%, and <50 copies/mL was 74%. These rates were similar between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients. The results were obtained using the Week 48 VL data and considering missing as failure.

2. The Week 48 median VL drop from baseline was 3.0-3.3 copies/mL in the ART-naïve or very limited ART exposed pediatric patients. Majority of the ART-experienced subjects maintained their virologic suppression through Week 48.

3. At Week 48, the overall increase from baseline in CD4+ cell count was 205 cells/mm^3 (range: -945, +1621). Change from baseline in CD4+ cell count was statistically significantly different between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients. The ART-experienced subjects had a median CD4+ decline of 72 cells/mm^3, while the ART-naïve or very limited ART exposed pediatric patients had median CD4+ increase between 201 and 330 cells/mm^3.

4. At Week 48, the overall increase from baseline in CD4% was 9% (range: -16%,34%). Change from baseline in CD4% was statistically significantly different between the ART-experienced subjects (median increase in CD4%=3%) and the ART-naïve or very limited ART exposed pediatric patients where the median CD4% increases from baseline were 11%, 8% and 13%, respectively, for the FTC-203/211/202 groups.

There are two statistical issues related to this NDA review.

<u>1. Estimation of the Primary Efficacy Endpoints Combining Three Studies in the Presence of Different Data Structures</u>

As we mentioned before, the FTC-202 (PACTG-1021) is conducted by the PACTG and sponsored by the DAIDS, NIAID, NICHD under a PACTG IND, while the FTC-203 and the FTC-211 are sponsored by Gilead Science Inc. There are protocol differences regarding the definitions of primary efficacy endpoints. Originally, most of the FTC pediatric studies except for the FTC-202 were submitted to the FDA on March 29, 2005. The FTC-202 datasets were finally submitted on August 1, 2005 per review team's requests. Because the data structure in FTC-202 was different from the other two studies, only rates based on snap-shots at Week 48 were obtained.

The primary efficacy endpoints were defined as proportions of subjects with viral load below the lower limit of quantification (LLOQ) at Week 48. The LLOQ values are 400 copies/mL and 50 copies/mL, respectively, for the Roche Amplicor HIV-1 Monitor™ Test (the Standard assay) and

the Roche Roche UltraSensitive Monitor™ Test (the Ultrasensitive assay).

Table 9 shows the overall proportions of subjects with virologic suppressions at Week 48. Overall, the viral load suppression to undetectable levels below LLOQ=400 and 50 copies/mL were 87% (n=147) and 74% (n=125) subjects in the ITT population (n=169).

2. Discrepancies and Similarities in Estimating of Primary Endpoints: TLOVR versus Cross-sectional Approaches

Table 9 also provides proportions of subjects with virologic suppressions at Week 48 by study and ART at baseline. Among 116 subjects in the FTC-203 ITT population, 88% (n=102) and 76% (n=88) had virologic suppression at Week 48, respectively, by the cross-sectional approach with LLOQ=400 copies/mL and LLOQ=50 copies/mL. These results are similar to 90% (n=104) and 74% (n=86) by the TLOVR approach, respectively, with LLOQ=400 copies/mL and LLOQ=50 copies/mL (see Table 7). The differences by the two methods were around 2%. In contrast, the results by the two approaches for FTC-211 are not comparable. Using LLOQ=400 copies/mL as an example, the proportion of subjects with virologic response at Week 48 were 94% and 69%, respectively, by the snap shot and the TLOVR approaches. The discrepancy indicates that at least 25% of the subjects had virologic rebound before Week 48 but their viral load became <400 copies/mL at Week 48. Because of the small sample size for the FTC-211 (n=16), the 25% difference between the two approaches could be by chance alone.

2. INTRODUCTION

2.1 Overview

This is a statistical review of the New Drug Application, NDA 21-896, for the accelerated approval of EMTRIVA® (Emitricitabine) oral solution in the treatment of HIV-infected pediatric patients.

During the review of NDA 21-896, it was decided by the review team to have a joint clinical/statistical review. Thus, efficacy results obtained by this reviewer were combined with clinical review by Russell Fleischer, PA-C, MPH in a joint review document.

The current document is a revised version of statistical review.

- One may find minor differences between the two. It was mainly due to the differences in estimating the baseline VL, CD4+ cell count and CD4% and in defining time windows. For example, a baseline value was previously defined as the mean value prior to Day 1 in the joint review. In this document, a baseline value was the most recent value prior to and at Day 1, similar to the definition by the sponsor.

- One may also find minimal differences in Week 48 efficacy results between this reviewer's and the sponsor's. This reviewer's results were sensitivity analyses to verify the sponsor's efficacy results. Different approaches and different statistics may be used.

2.2 Data Sources

The web addresses of the FTC-203/211/202 datasets in the CDER Electronic Document Room (EDR) are N21896\N_000\2005-03-29\crt\datasets\203, N21896\N-000\2005-03-29\crt\datasets\211 and N21896\N_000\2005-08-01\crt\datasets\202, respectively. The web address for the study report and efficacy summary can be found in N21986\2005-03-29\clinistat.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

For detailed study design; primary and secondary efficacy endpoints; demographic and baseline characteristics; patient disposition; statistical methodology used; applicant's results; please refer to the joint clinical/statistical review with Russell Fleischer, PA-C, MPH.

In this review document, this reviewer conducted sensitivity analyses for the following virologic suppression and immunological responses:

- Change from baseline in HIV-1 RNA (log_{10} copies/mL) through Week 48.
- Change from baseline in CD4+ cell count (cells/mm^3) and CD4% through Week 48.
- Percentage of subjects with virologic suppression through Week 48.
- Percentage of subjects with virologic suppression at Week 48.

All the above analyses were performed by the three FTC pediatric studies and by subjects' ART at baseline in the FTC-203. The FTC-211 has one subject with ART-experience at baseline. We performed the above analyses for the FTC-211 subjects as an ART naïve or very limited ART experienced group.

Efficacy Endpoints

Following are protocol defined primary efficacy endpoints.

The primary endpoints for the FTC-203 are the proportions of patients with suppression of plasma HIV-1 RNA to below the LLOQ for the assay, i.e., ≤ 400 and ≤ 50 copies/mL, for the Standard and Ultrasensitive tests, respectively, at Week 48, evaluated using non-completer=failure (NC=F) analysis.

The primary efficacy endpoint for the FTC-211 is the proportion of patients with suppression of plasma HIV-1 RNA to below the LLOQ ≤ 50 copies/mL for the Ultrasensitive tests at Week 48, evaluated using non-completer=failure (NC=F) analysis.

For the FTC-203/211, responder analyses were also conducted using the FDA-defined TLOVR algorithm.

The primary efficacy endpoint for the FTC-202 are the proportion of patients with suppression of plasma HIV-1 RNA to below the LLOQ, i.e, <400 and <50 copies/mL for the Standard and

Ultrasensitive tests at Week 16 and all other time points, evaluated using missing (for any reason) as a failure (M=F) for the Week 48 analysis.

Secondary efficacy endpoints for the FTC-203/211 are as follows:

1. The change from baseline in HIV-1 RNA levels at the measured time points (in ART-naïve patients only in FTC-203).
2. The change from baseline in CD4+ cell count (absolute and percent) at the measured time points and age-adjusted analysis of the change in CD4+ in the FTC-203.
3. The incidence of virologic failure (protocol-defined and TLOVR-defined) by Week 48.
4. In FTC-203, the incidence of patients experiencing clinical disease progression by Week 48.

Secondary efficacy endpoints for the FTC-202 are as follows:

1. The change from baseline in HIV-1 RNA levels at the measured time points.
2. The change from baseline in CD4+ cell count (absolute and percent) at the measured time points.
3. The incidence of virologic failure, probability of virologic failure estimated using the Kaplan-Meier method.

Patient Disposition, Demographic and Baseline Characteristics

Table 1 shows demographic information and baseline characteristics by study for Intention-to-treatment (ITT) population, defined as those who did not sign withdrew consent prior to treatment. Overall, there are 169 subjects in the ITT population, patients had a mean age of 7.9 years (range 0.3–21), 49% were male, 15% Caucasian, 61% Black and 24% Hispanic or other ethnic origins. Patients had a median baseline HIV RNA of 4.5 $\log_{10}$ copies/mL (range 1.7–5.9) and a median baseline CD4 cell count of 675 cells/mm^3 (range 2 – 2650).

At baseline, 89% (n=40) of the ART-experienced subjects in the FTC-203 trial had virological suppression, i.e., their baseline VL <400 copies/mL. In the sensitivity analyses, we conducted analyses of each parameter by the following four groups:
1) FTC-203: ART-naïve subjects;
2) FTC-203: ART-experienced subjects;
3) FTC-211; and
4) FTC-202.
Subgroup with baseline ART-naïve or ART-limited refers to subjects in 1), 3) and 4) although there is one ART-experienced subject in the FTC-211.

Table 1: Demographic and Other Baseline Characteristics by Study

Characteristic	FTC-203	FTC-202	FTC-211	Total
ITT Population n	116	37	16	169
Ethnic origin n (%)				
Black	80 (69.0)	23 (62.2)	0 (0)	103 (60.9)
Hispanic	n/a	9 (24.3)	0 (0)	9 (5.3)
White	4 (3.4)	5 (13.5)	16 (100)	25 (14.8)
Other	32 (27.6)[b]	0 (0)	0 (0)	32 (18.9)
Gender n(%)				
Female	61 (52.6)	17 (46.0)	8 (50)	86(50.9)
Male	55 (47.4)	20 (54.1)	8 (50)	83(49.1)
Age (yr)				
mean (std)	5.8 (3.2)	11.6 (6.0)	14.1 (0.7)	7.9 (4.9)
range	0.3-15.9	3.2-21.1	12.8-15.2	0.3-21.1
ART experience n (%)				
ART-naïve	71 (61.2)	37 (100.0)	15 (93.8)	123 (72.8)
ART experienced	45 (38.8)		1 (6.3)	46 (27.2)
HIV-1 RNA				
<400 copies/mL	40 (34.5)		0 (0)	40 (23.7)
≥400 copies/mL	76 (65.5)	37 (100.0)	16 (100)	129 (76.3)
Median (range)	5.0 (2.6,5.9)[a]	4.7 (3.6,6.4)[a]	4.9 (3.8,5.5)[a]	4.6 (1.7,6.4)[b]
CD4+ Cell Count (Cells/mm^3) Median (range)				
ART-naïve	714 (186,1886)	310 (2,1893)	373 (266,1100)	675 (2,2650)[b]
ART experienced	1045 (360,2650)			
CD4% Median (range)				
ART-naïve	19.5 (6.6,37.9)	17 (1,40)	23 (16,38)	23 (1,50.6)[b]
ART experienced	32.9 (10.9,50.6)			
History of HIV-related Event n (%)				
CDC Clinical Category N	15 (12.9)	3 (8.1)	0 (0)	18 (10.7)
CDC Clinical Category A	32 (27.6)	22 (59.5)	4 (25)	58 (34.3)
CDC Clinical Category B	47 (40.5)	7 (18.9)	8 (50)	62 (36.7)
CDC Clinical Category C	22(19.0)	5 (13.5)	4 (25)	31 (18.3)

a. For those who had baseline HIV RNA ≥400 copies/mL.
b. Overall results.

Statistical Methodologies

For the TLOVR analyses of virological suppression through Week 48, this reviewer used the DAVDP suggested TLOVR algorithm. The cross-sectional analyses of virological suppression at Week 48 considered VL missing as failure. All other efficacy analyses such as the change from baseline in VL, CD4+ cell count and CD4% were 'AS IS' approaches, meaning no imputations were applied.

Results and Conclusions

Please refer to the joint clinical/statistical review for the applicant's results and conclusion. This reviewer verified the applicant's VL, CD4+ cell count and CD4% data, and found these data in the electronic submissions were accurately matched with the study report. The minor discrepancies between this reviewer's and the sponsor's were caused by just a few data points.

Plasma HIV-1 RNA

In FTC-203, plasma HIV-1 RNA viral load (VL) was obtained using Roche UltraSensitive Monitor™ Test version 1.5 (v1.5) and v1.0 (the Ultrasensitive assay) and Roche Amplicor HIV-1 Monitor™ Test v1.5 and v1.0 (the Standard assay). The lower limits of detection (LLOD) are 400 copies/mL and 50 copies/mL, and the upper limits of detection (ULOD) are 750,000 copies/mL and 75,000 copies/mL, respectively, for the Standard assay and the Ultrasensitive assay.

The FTC-203 database shows that 49.86% of the VL values were measured by the Ultrasensitive v1.0 assay, 22.37% by the Ultrasensitive v1.5, 22.67% by the Standard v1.0 assay and 5.19% by the Standard v1.5 assay. When different assay methods were used in a study visit, the HIV RNA value was determined by the first non-missing value in the Ultrasensitive v1.0, followed by the Ultrasensitive v1.5, the Standard v1.0 and the Standard v1.5. For example, if a subject's VL vector by the four assays is (missing, 246, <400, missing), then this subject's VL would be 246 copies/mL.

- The follow-up visits for plasma HIV-1 RNA were scheduled at screening, day 1, Week 4, every 4 weeks thereafter until Week 96, and every 12 weeks after Week 96.

- The baseline HIV RNA was defined as the VL measurements at the baseline date (Day 1). If the VL at Day 1 is missing, the last non-missing value prior to first dose date was replaced.

- The date of sample collection (coldt) was used to determine the time window since baseline.

The baseline VL values in the FTC-203 were verified by this reviewer. All baseline values were matched with the sponsor's except for one female subject PATID=203-0443-0109, where the value of 324 cp/mL 15 days prior to Day 1 was used as baseline value. Her baseline value according to the rules should be 803 cp/mL at Day 1.

In the FTC-211 laboratory database, 39.6% of the VLs were measured by the v1.5 of the Uultrasensitive assay and 60.4% were measured by the v1.5 Standard assay. Most subjects had multiple HIV RNA measurements at the baseline date (Day 1). The date of sample collection (coldt) was used to determine the time window since baseline. For most subjects, plasma HIV-1 RNA values were at Weeks 0, 2, 4 and every 4 weeks thereafter until Week 48.

In the FTC-202 laboratory database, 48.9% of the VLs (range: 7-1,459,598 copies/mL) were measured by the v1.0 assay and 51.1% (range: 5-2,584,038 copies/mL) were measured by the v1.5 assay. Follow-up weeks (VIDVAL) in the plasma HIV-1 RNA databases were 0, 2, 4 every 4 weeks thereafter until Week 180. Most subjects had more than one HIV RNA measurements at the baseline date (VIDVAL=0). The last non-missing value at Week 0 was used as baseline value since there is no

baseline date available in the databases. Most of the subjects had VL measurements at Week 0, 2, 4, 8, 12 and every 12 weeks until Week 156.

Change from Baseline HIV RNA

The basic statistics of change from baseline HIV RNA in log10 copies/mL by follow-up week were summarized in Table 2 for the FTC-203, in Table 3 for the FTC-211/202, and in Table 4 for the three studies combined. For the FTC-203, VLs by ART status at baseline were also summarized.

Figure 1 shows median change from baseline HIV-1 RNA in $\log_{10}$ copies/mL by study and the ART status at baseline. It appears that the ART-experienced subjects in the FTC-203 had maintained their VL level, and the ART-naïve subjects in the FTC-203/202/211 had a median drop of 2.0 at Week 4, 3.0 after Week 16, and maintained their VL level through Week 48. The median VL drop for subjects in the FTC-211 was between 2-3 copies/mL. The three median curves in the ART naïve or very limited antiretroviral exposed patients were very close to each other. Please note that the median values were obtained using the sponsor's time window definitions of the follow-up visits for VL.

At Week 48, the median VL drops were 3.2, 3.0 and 3.3 cp/mL, respectively, for the FTC-203 (ART naïve subjects), FTC-211 and FTC-202. Overall, the ITT population (n=169) had a median VL drop of 2.9 cp/mL.

FTC-203/211/202

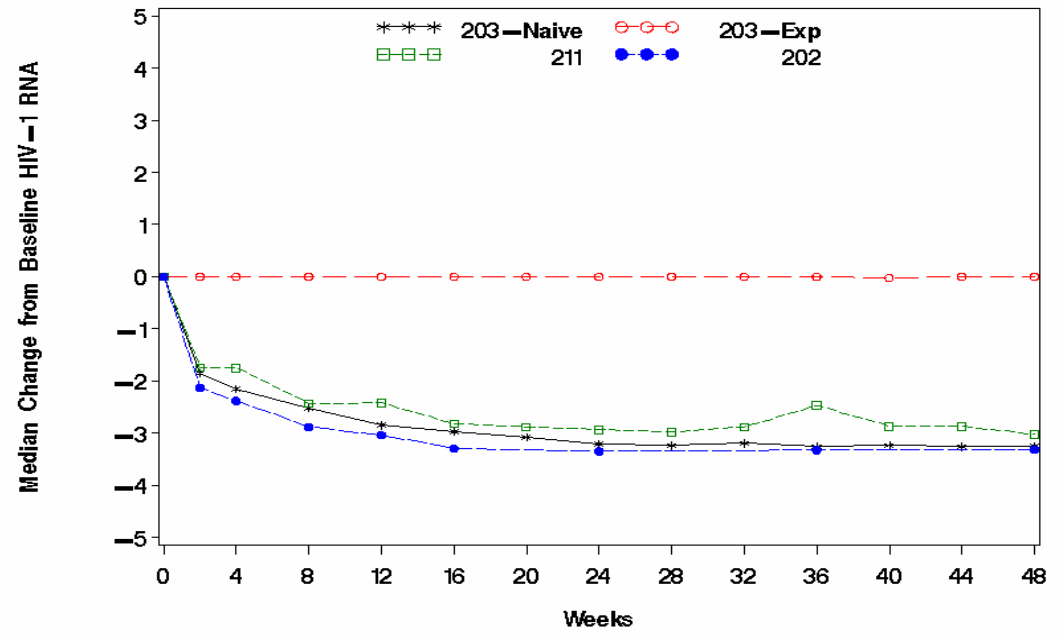

Figure 1: FTC-203/211/202: Median Change from Baseline HIV RNA (log10 copies/mL)

Table 2: FTC-203: Change from Baseline HIV RNA (log10 copies/mL)

week@	n	min	max	mean	std	med	p25	p75
FTC-203: ART Naive								
0	71	3.8	5.9	5.0	0.5	5.0	4.6	5.4
4	62	-3.1	0.2	-2.1	0.6	-2.1	-2.4	-1.9
8	69	-3.9	0.1	-2.5	0.8	-2.5	-2.9	-2.2
12	69	-4.1	0.0	-2.7	0.8	-2.8	-3.2	-2.6
16	70	-4.1	-0.4	-2.9	0.7	-3.0	-3.3	-2.7
20	71	-4.0	-0.1	-3.0	0.7	-3.1	-3.4	-2.6
24	69	-4.1	-0.1	-3.0	0.8	-3.2	-3.5	-2.7
28	65	-4.2	-0.7	-3.1	0.7	-3.2	-3.6	-2.7
32	68	-4.2	-1.1	-3.1	0.6	-3.2	-3.6	-2.8
36	66	-4.2	-0.8	-3.1	0.7	-3.3	-3.6	-2.7
40	66	-4.2	-0.6	-3.2	0.6	-3.2	-3.6	-2.8
44	64	-4.2	-1.0	-3.2	0.6	-3.3	-3.6	-2.8
48	64	-4.2	-2.0	-3.2	0.5	-3.2	-3.6	-2.8
FTC-203: ART Experienced								
0	45	1.7	3.7	2.1	0.5	1.7	1.7	2.6
4	42	-1.2	1.0	-0.2	0.6	0.0	-0.9	0.0
8	44	-1.0	1.4	-0.3	0.5	0.0	-0.9	0.0
12	43	-1.2	0.9	-0.3	0.5	0.0	-0.9	0.0
16	42	-1.2	0.9	-0.3	0.5	0.0	-0.9	0.0
20	41	-1.2	0.8	-0.3	0.5	0.0	-0.9	0.0
24	43	-1.2	1.0	-0.3	0.5	0.0	-0.9	0.0
28	42	-1.2	1.7	-0.2	0.6	0.0	-0.9	0.0
32	43	-1.2	2.4	-0.3	0.7	0.0	-0.9	0.0
36	40	-1.2	0.8	-0.3	0.5	0.0	-0.9	0.0
40	42	-1.2	0.9	-0.3	0.5	0.0	-0.9	0.0
44	39	-1.0	0.7	-0.3	0.5	0.0	-0.9	0.0
48	40	-1.2	0.9	-0.3	0.5	0.0	-0.9	0.0
Total								
0	116	1.7	5.9	3.9	1.5	4.5	2.6	5.2
4	104	-3.1	1.0	-1.3	1.1	-1.8	-2.2	0.0
8	113	-3.9	1.4	-1.6	1.3	-2.1	-2.6	-0.3
12	112	-4.1	0.9	-1.7	1.4	-2.4	-3.0	-0.1
16	112	-4.1	0.9	-1.9	1.4	-2.6	-3.1	-0.5
20	112	-4.0	0.8	-2.0	1.4	-2.5	-3.2	-0.5
24	112	-4.1	1.0	-2.0	1.5	-2.6	-3.3	-0.1
28	107	-4.2	1.7	-2.0	1.5	-2.6	-3.3	-0.5
32	111	-4.2	2.4	-2.0	1.5	-2.7	-3.3	-0.5
36	106	-4.2	0.8	-2.0	1.5	-2.6	-3.4	-0.8
40	108	-4.2	0.9	-2.1	1.5	-2.8	-3.3	-0.5
44	103	-4.2	0.7	-2.1	1.5	-2.8	-3.3	-0.8
48	104	-4.2	0.9	-2.1	1.5	-2.8	-3.4	-0.9

@. Week=0: baseline VL.

Table 3: FTC-211/202: Change from Baseline HIV RNA (log_{10} copies/mL)

week@	N	min	max	mean	std	med	p25	p75
FTC-211								
0	16	4.0	5.7	4.8	0.5	4.9	4.3	5.2
2	14	-2.7	-1.1	-1.8	0.4	-1.7	-2.1	-1.5
4	15	-2.9	-1.4	-1.9	0.4	-1.8	-2.1	-1.5
8	15	-3.3	-1.9	-2.5	0.4	-2.4	-2.8	-2.2
12	15	-3.8	-1.7	-2.5	0.5	-2.4	-2.7	-2.3
16	15	-4.0	-1.3	-2.8	0.6	-2.8	-3.2	-2.4
20	15	-4.1	-1.6	-2.8	0.6	-2.9	-3.2	-2.4
24	14	-4.1	-2.3	-2.9	0.5	-2.9	-3.2	-2.5
28	15	-4.1	-1.1	-2.9	0.7	-3.0	-3.5	-2.4
32	15	-4.1	-1.0	-2.7	0.8	-2.9	-3.2	-2.4
36	14	-4.1	-1.9	-2.6	0.7	-2.5	-3.0	-2.1
40	14	-4.1	-2.0	-2.9	0.6	-2.9	-3.4	-2.4
44	14	-4.1	-2.3	-3.0	0.5	-2.9	-3.4	-2.5
48	15	-4.1	-2.3	-3.1	0.5	-3.0	-3.5	-2.5
FTC-202								
0	37	3.6	6.4	4.7	0.6	4.7	4.3	5.2
2	36	-3.7	-1.0	-2.1	0.4	-2.1	-2.3	-1.9
4	36	-4.2	-0.3	-2.4	0.6	-2.4	-2.7	-2.1
8	30	-4.2	-2.0	-2.9	0.6	-2.9	-3.3	-2.5
12	34	-4.5	-1.0	-3.1	0.6	-3.0	-3.4	-2.9
16	32	-4.9	0.8	-3.2	1.0	-3.3	-3.8	-2.7
24	34	-4.9	0.8	-3.1	1.2	-3.4	-3.8	-2.8
36	29	-4.8	-2.4	-3.5	0.7	-3.3	-4.0	-2.9
48	30	-4.8	-2.1	-3.4	0.7	-3.3	-4.0	-2.9

@. Week=0: baseline VL.

Table 4: FTC-203/211/202: Change from Baseline HIV RNA (log_{10} copies/mL)

week@	n	min	max	mean	std	med	p25	p75
0	169	1.7	6.4	4.2	1.3	4.6	2.9	5.2
2	159	-3.7	1.5	-1.5	0.9	-1.8	-2.1	-0.9
4	162	-4.2	1.0	-1.6	1.0	-2.0	-2.4	-0.9
8	158	-4.2	1.4	-1.9	1.2	-2.3	-2.9	-0.9
12	161	-4.5	0.9	-2.1	1.3	-2.6	-3.0	-0.9
16	159	-4.9	0.9	-2.3	1.4	-2.8	-3.3	-0.9
20	130	-4.1	0.8	-2.1	1.4	-2.6	-3.2	-0.9
24	160	-4.9	1.0	-2.3	1.5	-2.8	-3.4	-0.9
28	122	-4.2	1.7	-2.1	1.5	-2.6	-3.4	-0.9
32	127	-4.2	2.4	-2.1	1.5	-2.7	-3.3	-0.9
36	149	-4.8	0.8	-2.4	1.4	-2.8	-3.5	-0.9
40	122	-4.2	0.9	-2.2	1.4	-2.8	-3.3	-0.9
44	118	-4.2	0.7	-2.2	1.4	-2.8	-3.3	-0.9
48	149	-4.8	0.9	-2.5	1.4	-2.9	-3.5	-1.0

@. Week=0: baseline VL.

Change from Baseline CD4+ Cell Count

In the laboratory databases, the follow-up visits for CD4+ cell count and CD4% were seen at screening, weeks 4, 8, 12, and every 12 weeks after Week 12 and at the end of study for the FTC-203/211. The CD4+/CD4% follow-up visits for the FTC-202 were at Weeks 0, 4, 16, 24, and every 12 weeks after Week 24. The baseline CD4+ was determined by the one prior to Day 1. Using the criterion similar to that for VL, if a subject had multiple CD4+ values prior to baseline, the last non-missing value prior to first dose date was used.

- This reviewer verified the baseline CD4+ cell count and CD4% for the FTC203/211, all matched the sponsor's.

Table 5 shows basic statistics in change from baseline CD4+ cell count (cells/mm^3) by follow-up week for the FTC-202/211, and also by the baseline ART status for the FTC-203. Figure 2 shows median change from baseline CD4+ cell count by the four groups. The median CD4+ increases from 182 to 261 cells/mm^3 for subjects in the ART-naïve subjects in FTC-203, followed by 15-241 cells/mm^3 in the FTC-202, 135-231 cells/mm^3 in the FTC-211, and -99 to 45 cells/mm^3 for ART-experienced subjects in the FTC-203.

The overall median change from baseline in CD4+ cell count at Week 48 was 205 cells/mm^3.

Change from baseline in CD4+ cell count was statistically significantly different between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients, $p<0.001$ by the Kruskal-Wallis tests. The ART-experienced subjects had a median CD4+ decline of 72 cells/mm^3, while the ART-naïve or very limited ART exposed pediatric patients had median CD4+ increase of 201-330 cells/mm^3.

Change from Baseline CD4%

Table 6 shows basic statistics of the baseline CD4% and the change from baseline CD4% by follow-up week, ART at baseline for FTC-203, and those for FTC-211 and FTC-202. Figure 3 shows median change from baseline in CD4% by study and ART at baseline. The temporal patterns are similar between CD4+ and CD4%. Subjects in the ART-naïve subjects in FTC-203 had a median increase between 8-13%, followed by median increase between 5-12% in the FTC-202, 6-8% in the FTC-211, and 2-4% for ART-experienced subjects in the FTC-203.

At Week 48, the overall increase from baseline in CD4% was 9% (range: -16%,34%). The change from baseline in CD4% was statistically significantly different between the ART-experienced subjects (median increase in CD4%=3%) and the ART-naïve or very limited ART exposed pediatric patients where the median CD4% increases from baseline were 11%, 8% and 13%, respectively, for the FTC-203/211/202 groups, $p<0.001$ by the Kruskal-Wallis test.

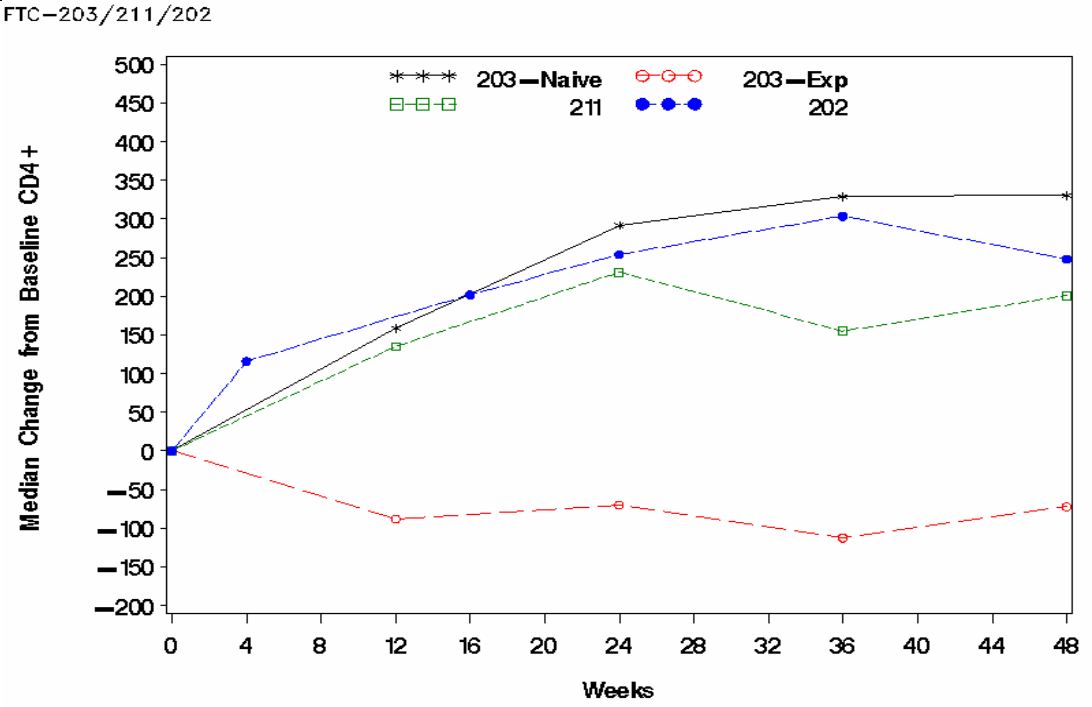

Figure 2: FTC203/211/202: Median Change from Baseline CD4+ Cell Count (cells/mm3)

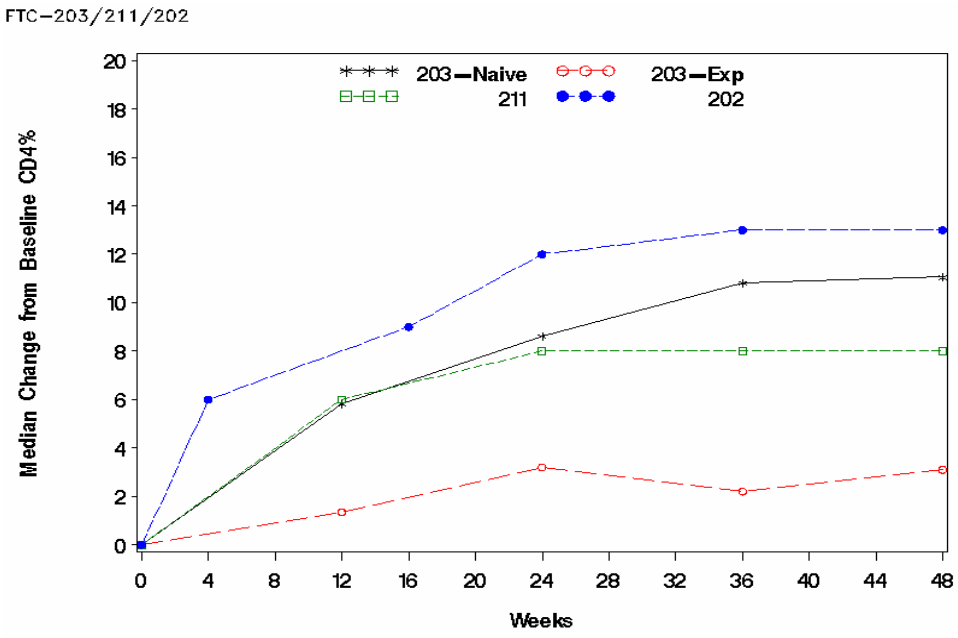

Figure 3: FTC203/211/202: Median Change from Baseline CD4%

Table 5: FTC-203/211/202: Change from Baseline CD4+ Cell Count (cells/mm^3)

week@	n	min	Max	Mean	std	med	p25	p75
FTC-203-ART Naive								
0	71	186	1886	772	420	714	432	944
12	70	-647	2266	239	430	159	16	471
24	67	-705	1625	283	355	292	91	425
36	67	-683	1395	326	383	329	68	510
48	67	-512	1621	344	372	330	98	503
FTC-203-ART Experienced								
0	44	360	2650	1100	490	1045	772	1387
12	43	-640	482	-99	224	-88	-225	27
24	42	-849	691	-56	283	-70	-233	103
36	40	-897	734	-103	313	-113	-243	24
48	41	-945	712	-19	283	-72	-158	175
FTC-203-Total								
0	115	186	2650	898	474	817	533	1121
12	113	-647	2266	111	400	53	-123	264
24	109	-849	1625	152	367	121	-65	331
36	107	-897	1395	165	414	140	-120	449
48	108	-945	1621	206	383	176	-63	428
FTC-202								
0	37	2	1893	386	377	310	169	419
4	32	-144	634	132	152	116	60	173
16	32	66	639	222	124	202	132	280
24	33	-1	606	257	146	254	138	348
36	26	11	500	275	128	304	198	360
48	31	-612	1308	273	314	248	169	359
FTC-211								
0	16	266	1100	479	245	373	323	546
12	15	-92	516	137	177	135	-26	214
24	15	-443	577	211	235	231	104	352
36	14	-110	461	174	174	155	66	337
48	15	-107	366	164	157	201	25	301
FTC-203/202/211								
0	168	2	2650	745	491	675	362	1020
4	32	-144	634	132	152	116	60	173
12	128	-647	2266	114	381	64	-94	262
16	32	66	639	222	124	202	132	280
24	157	-849	1625	180	324	152	-11	338
36	147	-897	1395	186	363	207	-31	384
48	154	-945	1621	216	354	205	11	380

@. Week=0: baseline CD4+.

Table 6: FTC-203/211/202: Change from Baseline CD4%

week@	n	min	Max	Mean	std	med	p25	p75
FTC-203-ART Naive								
0	71	7	38	21	7	20	15	26
12	70	-8	17	6	6	6	2	11
24	67	-4	23	8	6	9	5	12
36	67	-4	28	11	6	11	7	14
48	67	-5	34	12	7	11	7	16
FTC-203-ART Experienced								
0	44	11	51	33	8	33	29	38
12	43	-6	9	1	3	1	-1	3
24	42	-5	10	3	4	3	-1	6
36	40	-9	11	2	4	2	-1	4
48	41	-11	13	3	5	3	1	7
FTC-203-Total								
0	115	7	51	26	9	25	18	33
12	113	-8	17	4	6	3	0	8
24	109	-5	23	6	6	6	2	10
36	107	-9	28	7	7	7	3	12
48	108	-11	34	8	7	8	3	13
FTC-202								
0	37	1	40	17	10	17	10	23
4	32	-3	36	7	7	6	4	10
16	32	2	22	10	5	9	6	13
24	33	-3	24	11	5	12	7	15
36	27	1	28	14	7	13	9	20
48	31	-16	27	13	8	13	9	18
FTC-211								
0	16	16	38	25	8	23	19	30
12	15	-5	15	7	5	6	5	11
24	15	2	22	9	5	8	5	9
36	19	3	27	10	7	8	7	12
48	15	3	29	11	7	8	5	15
FTC-203/202/211								
0	168	1	51	24	10	23	16	31
4	32	-3	36	7	7	6	4	10
12	128	-8	17	4	5	4	1	8
16	32	2	22	10	5	9	6	13
24	157	-5	24	7	6	7	4	12
36	153	-9	28	9	7	9	4	13
48	154	-16	34	10	8	9	4	14

@. Week=0: baseline CD4%.

Treatment Outcomes (TLOVR) at Week 48

Table 7 summarizes the outcomes through Week 48/96 in the FTC-203/211. Table 8 shows the outcomes through Week 48/96 by baseline ART in the FTC-203. Except for two subjects who had rebound time within Week 48 time window and were classified as 'rebounder' by this reviewer, all the frequencies were similar to those from the sponsor's.

Table 7: FTC-203/211: Summary of TLOVR-Defined Outcome of FTC Treatment

Outcome	FTC-203 N=116	FTC-211 n=16
Completed study through Week 48	**109 (94)**	**15 (94)**
LOQ = 400 copies/mL		
Virological Responders[1]	104 (90)	11 (69)
No confirmed response	1 (1)	0 (0)
Rebound	4 (3)	4 (25)
LOQ = 50 copies/mL		
Virological Responders[1]	86 (74)	10 (63)
No confirmed response[3]	5 (4)	2 (13)
Rebound	18 (16)	3 (19)
Not completed study through Week 48	**7 (6)**	**1 (6)**
Death or discontinuation due to AE	2 (2)	0 (0)
Discontinuation due to other reasons[2]	5 (4)	1 (6)
Completed study through Week 96	**69 (59)**	
LOQ = 400 copies/mL		
Virological Responders[1]	65 (56)	
No confirmed response	0 (0)	
Rebound	4 (3)	
LOQ = 50 copies/mL		
Virological Responders[1]	50 (43)	
No confirmed response	2 (2)	
Rebound	17 (15)	
Not completed study through Week 96	**47 (41)**	
Death or discontinuation due to AE	2 (2)	
Discontinuation due to other reasons	45 (39)	

Table 8: FTC-203: Summary of TLOVR-Defined Outcome through Week 48

Outcome	Naive N=71	Experienced N=45	Total n=116
Completed study through Week 48	**67 (96)**	**42 (93)**	**109 (94)**
LOQ = 400 copies/mL			
Virological Responders[1]	66 (93)	38 (84)	104 (90)
No confirmed response	1 (1)	0 (0)	1 (1)
Rebound	0 (0)	4 (9)	4 (3)
LOQ = 50 copies/mL			
Virological Responders[1]	56 (79)	32 (71)	88 (76)
No confirmed response	2 (3)	3 (4)	5 (4)
Rebound	9 (13)	7 (10)	16 (14)
Not completed study through Week 48	**4 (6)**	**3 (7)**	**7 (6)**
Death or discontinuation due to AE	1 (1)	1 (2)	2 (2)
Discontinuation due to other reasons	3 (4)	2 (4)	5 (4)
Completed study through Week 96	**44 (62)**	24 (53)	**68 (59)**
LOQ = 400 copies/mL			
Virological Responders[1]	44 (62)	20 (44)	64 (55)
No confirmed response	0 (0)	0 (0)	0 (0)
Rebound	0 (0)	4 (9)	4 (3)
LOQ = 50 copies/mL			
Virological Responders[1]	35 (49)	17 (38)	52 (45)
No confirmed response	0 (0)	**2 (4)**	2 (2)
Rebound	9 (13)	5 (11)	14 (12)
Not completed study 48-96 week	**27 (38)**	21 (47)	**48 (41)**
Death or discontinuation due to AE	1 (1)	1 (2)	2 (2)
Discontinuation due to other reasons	6 (8)	6 (13)	12 (10)
Virological Responders	19 (27)	13 (29)	32 (28)
No confirmed response	1 (1)	0 (0)	1 (1)
Rebound	0 (0)	1 (2)	1 (1)

1 Patients maintained confirmed HIV RNA ≤ LOQ through Week 48 or 96.
2 Includes lost to follow-up, patient's withdrawal and other reasons.

Probability of LOVR Curves (Kaplan-Meier) for FTC-203

Figure 4 below shows the Kaplan-Meier probability of loss of virologic response (LOVR) curves through Week 48/96 by LLOQ. The estimated probabilities of LOVR at Week 48 are 24.1% and 10.3%, respectively for LLOQ=50 cp/mL and 400 cp/mL. The estimated probabilities of LOVR at Week 96 are 38.0% and 23.7%, respectively for LLOQ=50 cp/mL and 400 cp/mL.

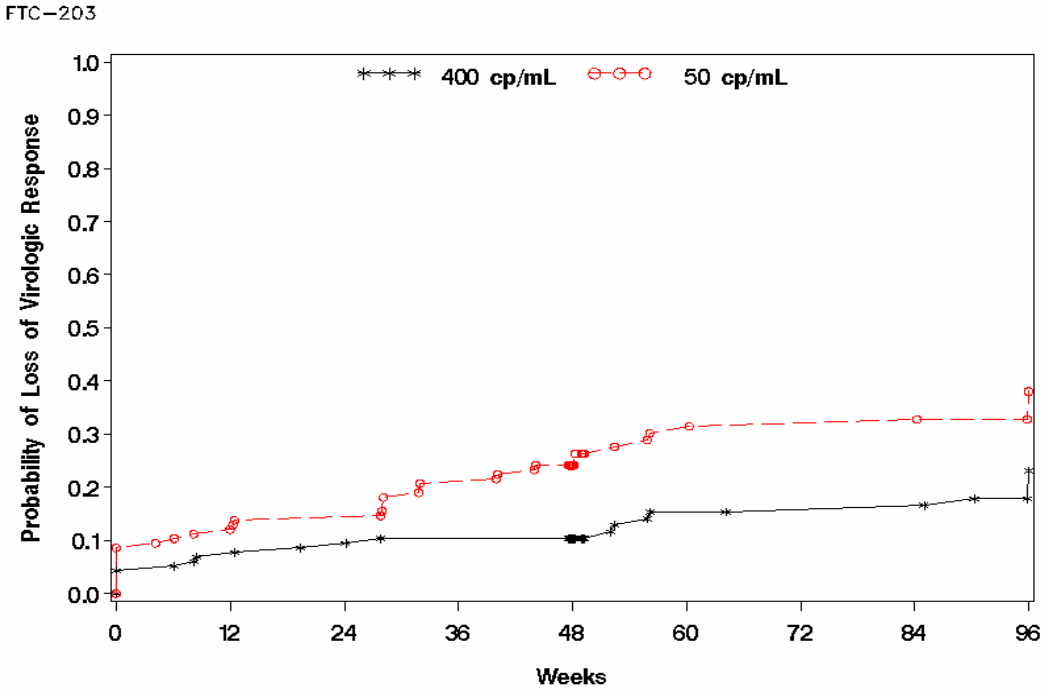

Figure 4: FTC-203: K-M Loss of Virologic Response by LLOQ

Proportion of Subjects with Viral Load below LLOQ at Week 48

In a sensitivity analysis, this reviewer obtained proportion of subjects who were virologically suppressed at Week 48, using the VL data from the three FTC studies. Subjects whose VL values at Week 48 were missing due to discontinuation or other reasons were considered as failure. Time window for the Week 48 is between 323 and 350 days since Day 1. Table 9 shows the results.

Table 9: Proportion of Subjects with IHV-1 RNA < LLOQ at Week 48

ITT Population	N	LLOQ=400 cp/mL N (%)	LLOQ=50 CP/mL N (%)
FTC-203 ART-Naïve	71	63 (88.7)	53 (74.7)
FTC-203 ART-Experienced	45	39 (86.7)	35 (77.8)
FTC-211	16	15 (93.8)	10 (62.5)
FTC-202	37	30 (81.1)	27 (73.0)
Total	169	147 (87.0)	125 (74.0)

3.2 Evaluation of Safety

Please refer to the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Please refer to the medical officer's review in the joint clinical/statistical review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following are findings regarding the emtricitabine efficacy endpoints.

1. Through 48 weeks of therapy, the overall proportion of patients who achieved and sustained an HIV RNA <400 copies/mL was 87%, and <50 copies/mL was 74%. These rates were similar between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients. The results were obtained using the Week 48 VL data and considering missing as failure.

2. The Week 48 median VL drop from baseline was 3.0-3.3 copies/mL in the ART-naïve or very limited ART exposed pediatric patients. Majority of the ART-experienced subjects maintained their virologic suppression through Week 48.

3. At Week 48, the overall increase from baseline in CD4+ cell count was 205 cells/mm^3 (range: -945, +1621). Change from baseline in CD4+ cell count was statistically significantly different between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients. The ART-experienced subjects had a median CD4+ decline of 72 cells/mm^3, while the ART-naïve or very limited ART exposed pediatric patients had median CD4+ increase between 201 and 330 cells/mm^3.

4. At Week 48, the overall increase from baseline in CD4% was 9% (range: -16%,34%). Change from baseline in CD4% was statistically significantly different between the ART-experienced subjects (median increase in CD4%=3%) and the ART-naïve or very limited ART exposed pediatric patients where the median CD4% increases from baseline were 11%, 8% and 13%, respectively, for the FTC-203/211/202 groups.

There are two statistical issues related to this NDA review.

<u>1. Estimation of the Primary Efficacy Endpoints Combining Three Studies in the Presence of Different Data Structures</u>

As we mentioned before, FTC-202 (PACTG-1021) is conducted by the PACTG and sponsored by the DAIDS, NIAID, NICHD under a PACTG IND, while the FTC-203 and the FTC-211 are sponsored by Gilead Science Inc. There are protocol differences regarding the definitions of primary efficacy endpoints. Originally, most of the FTC pediatric studies except for the FTC-202 were submitted to the FDA on March 29, 2005. The FTC-202 datasets were finally submitted on August 1, 2005 per review team's requests. Because the data structure in FTC-202 was different from the other two studies, only rates based on snap-shots at Week 48 were obtained.

The primary efficacy endpoints were defined as proportions of subjects with viral load below the lower limit of quantification (LLOQ) at Week 48. The LLOQ values are 400 copies/mL and 50 copies/mL, respectively, for the Roche Amplicor HIV-1 Monitor™ Test (the Standard assay) and the Roche Roche UltraSensitive Monitor™ Test (the Ultrasensitive assay).

Table 9 shows the overall proportions of subjects with virologic suppressions at Week 48. Overall, the viral load suppression to undetectable levels below LLOQ=400 and 50 copies/mL were 87% (n=147) and 74% (n=125) subjects in the ITT population (n=169).

2. Discrepancies and Similarities in Estimating of Primary Endpoints: TLOVR versus Cross-sectional Approaches

Table 9 also provides proportions of subjects with virologic suppressions at Week 48 by study and ART at baseline. Among 116 subjects in the FTC-203 ITT population, 88% (n=102) and 76% (n=88) had virologic suppression at Week 48, respectively, by the cross-sectional approach with LLOQ=400 copies/mL and LLOQ=50 copies/mL. These results are similar to 90% (n=104) and 74% (n=86) by the TLOVR approach, respectively, with LLOQ=400 copies/mL and LLOQ=50 copies/mL (see Table 7). The differences by the two methods were around 2%. In contrast, the results by the two approaches for the FTC-211 are not comparable. Using LLOQ=400 copies/mL as an example, the proportion of subjects with virologic response at Week were 94% and 69%, respectively, by the snap shot and the TLOVR approaches. The discrepancy indicates that at least 25% of the subjects had virologic rebound before Week 48 but their viral load became <400 copies/mL at Week 48. Because of the small sample size for the FTC-211 (n=16), the 25% difference between the two approaches could be by chance alone.

5.2 Conclusions and Recommendations

Emitricitabine in combination with other antiretroviral agents achieved virologic suppression rates in HIV-1 infected pediatric subjects that are consistent with those of the adult studies. No definitive efficacy conclusion can be reached for the oral solution of Emitricitabine since the studies were not controlled.

Based on analyses of the Week 48 data in the three single arm clinical studies FTC203, FTC-202 and FTC-211, the overall proportions of subjects had achieved virologic suppression were 87% and 74% for <400 copies/mL and <50 copies/mL, respectively. These rates were similar between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients. The overall median change from baseline in CD4+ cell count at Week 48 was 205 cells/mm^3. Change from baseline in CD4+ cell count was statistically significantly different between the ART-experienced subjects and the ART-naïve or very limited ART exposed pediatric patients: the ART-experienced subjects had a median CD4+ decline of 72 cells/mm^3, while the ART-naïve or very limited ART exposed pediatric patients had median CD4+ increase of 201-330 cells/mm^3.

Based on analyses of the Week 96 data in clinical the FTC203, 40.5% of the study subjects have discontinued the treatment. Most of the subjects (89.9%) remaining in the study continued their suppression of HIV-1 RNA at Week 96.

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