The major secondary endpoints included the proportion with HIV RNA <50 c/mL, virologic failure (defined as HIV-1 RNA >400 c/mL on two consecutive evaluations), efficacy failure (defined as virologic failure, CDC Class C progression, death, or lost to follow-up), effectiveness failure (defined as virologic failure, tolerability failure, CDC Class C progression, or lost to follow-up), and mean change from baseline of CD4+ cells. Table 4 presents the 48-week efficacy results for the groups whom switched to Emtriva® or remained on their 3TC-containing regimen.

Table 4. Outcomes of randomized treatment at Week 48.

	Emtriva+ZDV/d4T+NNRTI/PI (n=294)	Epivir®+ZDV/d4T+NNRTI/PI (n=146)
HIV RNA≤400 c/mL[1]	77%	82%
HIV RNA≤50 c/mL[2]	67%	72%
Virologic failure[3]	7%	8%
Death	0%	<1%
DC due to adverse events	4%	0%
DC due to other reasons[4]	12%	10%

1. Patients achieved and maintained confirmed HIV RNA <400 c/mL through Week 48.
2. Patients achieved and maintained confirmed HIV RNA <50 c/mL through Week 48.
3. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
4. Includes lost to follow-up, consent withdrawal, non-compliance, protocol violations, and other reasons.

The stratum-adjusted difference between the Emtriva and Epivir arms was –4.8% with a 95% confidence interval of -12.8% to 3.3%, numerically favoring remaining on 3TC.

Disease Progression

New CDC Class C events were considered evidence of disease progression. There was no difference between treatment arms with respect to the occurrence of new Class C events. Five patients experienced a new Class C event: two received Emtriva (Kaposi's sarcoma and mycobacterium infection) and three received 3TC (pneumocystis pneumonia, cervical cancer, and cytomegalovirus disease).

Thirteen Emtriva and 6 3TC-treated patients experienced new CDC Class B events. The events in the Emtriva arm included: seborrhea, tinea cruris, molluscum contagiosum, herpes zoster, herpes simplex (2), hairy leukoplakia (2), community acquired pneumonia (2), and peripheral neuropathy. The events in the 3TC arm included: seborrhea (2), herpes zoster, hairy leukoplakia, psoriasis, wasting syndrome, and oral thrush.

Virologic failure

The frequency of virologic failure, defined as HIV RNA >400 c/mL on two consecutive assessments, was comparable between treatment arms (see Table 4). Longitudinal comparisons of Kaplan-Meier curves for loss of virologic response (LOVR) demonstrated that a history of Combivir® (fixed dose ZDV+3TC) use and baseline HIV RNA >50 c/mL were associated with a greater risk of LOVR. No association between LOVR and other risk factors was identified.

Thirty-four patients experienced virologic failure (23 in Emtriva arm and 11 in 3TC arm). Genotypic analyses demonstrated a higher proportion of Emtriva-treated patients having evidence of a new M184V/I mutation, 17/19 (90%) versus 3/4 (75%) in 3TC failures. The numbers are small and do not include samples on all patients.

Immunologic Outcomes

At study entry, the mean baseline CD4 cell count was approximately 530 cells/mm^3 in both arms. Patients who remained on their 3TC-containing regimen experienced greater increases in absolute CD4 cell counts over the duration of the study, +61 cells/ mm^3 compared to +29 cells/mm^3 in the Emtriva arm. The median percent change in CD4 cells was +1.7% and +2.5% in the Emtriva and 3TC arms, respectively.

Proportion who remained on randomized therapy

A total of 23 (8%) Emtriva and 7 (5%) 3TC patients had at least one change of their study medication; the reasons for switching were similar between arms.

Assessment of Outcomes by Gender, Age and Ethnicity

Treatment by gender and treatment differences were observed with regard to LOVR. When stratified by treatment arm, male patients who switched to Emtriva had better virologic responses than female patients who switched. These findings may be accounted for by the higher frequency of discontinuations among female patients, 38% versus 19%. No gender difference was observed in the 3TC arm, and no treatment differences were observed in male patients in either treatment arm.

The statistical reviewer used a median age of 41 to categorize patients as younger (≤42) or older (>42). Overall, age >42 was associated with greater LOVR in both treatment arms. Younger patients in the 3TC treatment arm did better with respect to LOVR than those in the Emtriva treatment arm. No treatment difference was found for the older subjects.

Patients in three ethnic categories Caucasian, Black and Hispanic constituted 98% of the ITT study population. Overall, there were no significant treatment differences in LOVR between racial groups.

- **Overall Assessment of Study FTC-303**

Previous studies suggest that when 3TC is used as a component of triple antiretroviral therapy, 70% efficacy (HIV RNA <400 c/mL through 48 weeks) can be anticipated. In study FTC-303, this threshold was exceeded by nearly 10% in patients who mostly received over 2 years of 3TC-based therapy. Although patients who switched to Emtriva® also had better than 70% success, the immunologic results suggest that numerical efficacy was less than continued 3TC, although new CDC class B and C events were comparable. In addition, secondary endpoints such as effectiveness failure and mean change in CD4 cell counts demonstrated an advantage in favor of patients remaining on 3TC-based therapy.

Although the numbers of patients on whom samples were tested was small, genotypic analysis of patients who experienced rebound of viral load identified no difference in the frequency of the M184V/I mutation between Emtriva and 3TC.
The reason for the differential efficacy results may be related to the higher frequency of discontinuations from the Emtriva arm due to adverse events (patients may have been more likely to discontinue because of the impression that new adverse events may be related to the new drug), or possibly because of a desire of open label subjects not to be on a perceived inferior arm. Alternatively, some patients may have lost Emtriva potency because the molecule contains a negatively charged fluorine moiety that may have interacted less well with viral DNA than 3TC.

Compliance with study medication was comparable between treatment groups. At the time the study was initiated, it was theorized that Emtriva would provide a compliance advantage over 3TC because it would be administered once daily compared to twice daily for 3TC. Since the study was conducted, 3TC has been approved for once daily administration, thus eliminating any perceived dose frequency advantage for Emtriva.

C.1.b Study FTC-301A

"A Randomized, Double-Blind, Equivalence Trial Comparing Emtricitabine to Stavudine within a Triple Combination Containing Didanosine Plus Efavirenz in Antiretroviral-Drug Naïve HIV-1 Infected Patients."

This study was conducted between August 2000 and May 2002 in 101 centers in North America, Latin America, South America, and Europe.

- **Objectives**

The primary objective was to assess the safety and efficacy of Emtriva compared to stavudine (d4T) when used within a regimen containing didanosine (ddI) and efavirenz (EFV).

Secondary objectives included comparisons of (1) time to virologic failure; (2) time to effectiveness failure; (3) time to plasma HIV-1 RNA nadir; (4) change from baseline values in HIV-1 RNA. Other secondary objectives included a determination of the magnitude of CD4 cell count changes and percent increase above baseline and characterization of the reverse-transcriptase genotype from virologic failures.

- **Design**

FTC-301A was a phase 3, randomized, double blind, double-dummy, multi-center study to evaluate the equivalence of Emtriva to d4T when combined with ddI and EFV[2]. The study was to

[2] In May 1999, the applicant submitted the original protocol for study FTC-301, which proposed an open-label, randomized, multi-center study to determine superiority for FTC compared to abacavir (ABC) when combined with EFV and d4T in antiretroviral-naïve HIV-infected subjects. The Division provided a significant number of recommendations related to the design and analysis of the study (see Medical and Statistical reviews for IND : [redacted] serial 056, July 15, 1999). The applicant addressed a number of the minor recommendations but did not address the major study design deficiencies. The applicant subsequently initiated the study and enrolled approximately 40 patients. In January 2000, the

enroll 350 antiretroviral-naïve HIV-1 infected patients 18 years of age or older with baseline HIV RNA >5,000 c/mL and a CD4 cell count ≥200 cells/mm^3. Patients were randomized 1:1 to:

Arm 1: FTC (200 mg QD)+d4T placebo (BID)+ddI (400 mg QD)+EFV (600 mg QD)[3]
Arm 2: FTC placebo (QD)+d4T (40 mg BID)+ddI (400 mg QD)+EFV (600 mg QD)[3]

Randomization was stratified based on screening plasma HIV RNA, and previous participation in study FTC-301 as follows:

Stratum 1: antiretroviral-naïve with HIV RNA 5,000-100,000 c/mL
Stratum 2: antiretroviral-naïve with HIV RNA >100,000 c/mL
Stratum 3: patients previously enrolled in FTC-301 (n=27)

The study will continue until the last randomized patient completes 48 weeks of treatment. Patients whose viral load was <400 c/mL through the end of the study will be offered an open-label triple combination regimen containing Emtriva (study FTC-350).

Comment: At the time the study was designed, ddI+d4T was a commonly used first-line NRTI combination. Since then, the utility of this combination has waned because of an association with a high frequency of adverse events, which has led to lower than expected efficacy due to frequent discontinuations.

- **Demographics and Disposition**

A total 584 treatment-naïve HIV-1 infected male and female patients 18 years of age and older were enrolled: 294 to Emtriva and to 290 d4T. Of these, 286 and 285 received at least one dose of Emtriva or d4T, respectively.

The baseline characteristics demonstrated the study population to be 85% male, 52% Caucasian, 16% black, and 25% hispanic. The mean age was 36 years (range 18-69). The mean baseline HIV-RNA was 4.8 $\log_{10}$ c/mL (range 2.6-7.0 $\log_{10}$ c/mL), with 56% of patients having HIV RNA <100,000 c/mL. The mean CD4 cell count was 318 cells/mm^3 (range 5-1317 cells/mm^3). Eighteen percent and 3% had a history of a CDC class B or C AIDS-defining event at baseline.

Comment: The treatment arms were well balanced and represented a reasonably healthy population of treatment naïve patients.

Patient disposition is described in Table 5.

applicant proposed significant amendments to FTC-301, including changing the design from superiority to equivalence, changing from an open-label to double-blind design, and changing the comparator from ABC to d4T.

[3] Subjects weighing <60 kg received d4T 30 mg bid and ddI 250 mg QD.

Table 5. Patient disposition through 48 weeks.

	Emtriva®	d4T
Randomized	294	290
Received at least one dose*	286	285
Completed 48 weeks	237 (83%)	207 (73%)
Discontinued	49	78
Adverse event	16 (6%)	33 (12%)
Lost to follow-up	9 (3%)	12 (4%)
Non-compliance	2 (<1%)	3 (1%)
Virologic failure	8 (2%)	22 (8%)
Protocol violation	7 (2%)	2 (<1%)
Request withdrawal	5 (2%)	4 (1%)
Death	0	2 (<1%)
Other	2 (<1%)	2 (<1%)

*5 patients in each treatment group failed to return following their baseline visit.

Significantly more patients discontinued the d4T+ddI regimen due to adverse events; a finding that was not unexpected as this is a combination that is associated with clinically significant adverse effects.

- **Outcome Assessments and Results**

The primary endpoint was the proportion of patients with HIV RNA ≤400 c/mL at 48 weeks using a non-completer equals failure analysis.

The trial was powered to demonstrate that FTC would be equivalent to d4T. According to the sponsor, with a minimum sample size of 175 patients per arm there would be 80% power to detect a 10% difference in the proportion of patients with HIV RNA ≤50 c/mL between FTC and d4T at 24 and 48 weeks. Patients in Stratum 3 were analyzed separately.

Table 6 presents the 48-week results for the intent-to-treat population.

Table 6. Outcomes of randomized treatment at Week 48.

	Emtriva+ddI+EFV (n=294)	Zerit®+ddI +EFV (n=290)
HIV RNA≤400 c/mL[1]	81%	68%
HIV RNA≤50 c/mL[2]	78%	59%
Virologic failure[3]	3%	11%
Death	0%	<1%
DC due to adverse events	7%	13%
DC due to other reasons[4]	9%	8%

1. Patients achieved and maintained confirmed HIV RNA <400 c/mL through Week 48.
2. Patients achieved and maintained confirmed HIV RNA <50 c/mL through Week 48.
3. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
4. Includes lost to follow-up, consent withdrawal, non-compliance, protocol violations, and other reasons.

Immunologic Outcomes

Patients in the Emtriva arm experienced greater increases in absolute CD4 cell counts (+163 cells/mm^3 versus +139 cells/mm^3 and CD4% (+10% versus +6%).

Disease Progression

Occurrence of a new CDC Class C event was considered evidence of HIV disease progression. There were no significant differences between treatment groups. Five patients in the Emtriva arm (1.7%) and nine in the d4T arm (3.1%) had a new CDC Class C event on study. The events in the Emtriva arm included Kaposi's sarcoma (1), diarrhea due to Isospora belli (1), Mycobacterium tuberculosis (1), esophageal candidiasis (1), and herpes simplex virus (1).

In the d4T arm, the events included: pneumocystis carinii pneumonia with herpes simplex proctitis (1), wasting syndrome (4), diarrhea due to Cryptosporidium (1), esophageal candidiasis (1), and Kaposis sarcoma (2).

Virologic Failure

As presented in Table 6, more patients experienced virologic failures in the d4T arm compared to the Emtriva arm. Through 48 weeks, 58 patients had confirmed virologic failure, 17 in the Emtriva group and 41 in the d4T group. Six Emtriva failures had evidence of the M184V/I mutation compared to none in the d4T arm, an expected finding. More patients in the d4T group had evidence of resistance to EFV and thymidine analogue mutations. Genotypic mutations suggesting resistance to ddI was similar between treatment arms.

Assessment of Outcomes by Gender, Age and Ethnicity

Gender and treatment differences in the LOVR analysis were identified. Overall, males had better virologic responses than females. Further, females in the d4T treatment arm had lower virologic response than females in the Emtriva treatment arm. No significant treatment difference was observed in male subjects between the two treatment arms. Since overall only 15% of study participants were female, no additional conclusions could be reached.

Patients 35 years and older in the d4T treatment arm had worse virologic response than older patients in the Emtriva arm. No significant treatment effect in LOVR was observed among patients age < 35 years. Stratified by treatment arm, increased age was not associated with higher LOVR.

Stratified by treatment arm, Caucasians had the lowest LOVR, followed by Hispanics, and Blacks in the d4T treatment arm, but no difference was observed in the Emtriva arm. Stratified by race, Hispanics in the d4T treatment arm had greater LOVR compared to Hispanics in the Emtriva treatment arm.

Additionally, significant racial differences in LOVR were seen in patients with screening HIV RNA < 100,000 c/mL in the d4T treatment arm favoring Caucasians. Conversely, Hispanics with

screening HIV RNA < 100,000 c/mL had the best virologic outcomes in the Emtriva arm.

Assessment of study FTC-301A

The results of study FTC-301A demonstrate: (1) the virologic response was similar for the Emtriva arm and equivalent to the d4T reference arm; (2) the virologic response was sustained over 48 weeks; and (3) the virologic response was associated with a significant rise in CD4+ cell counts and CD4%. Discontinuations due to adverse events (patients were classified as treatment failures in the efficacy analyses) and more virologic failures from the d4T arm accounted for the differences in efficacy.

The results of study FTC-301A support a conclusion that an initial regimen in treatment naïve patients that includes Emtriva rather than the combination of d4T+ddI may be more tolerable and result in greater virologic success. These findings support the conclusion of other studies showing that regimens containing both lamviudine and efavirenz are extremely effective and that ddI+d4T is a more toxic nucleoside backbone and when combined with efavirenz, is associated with worse virologic outcomes (preliminary results of ACTG 384). Given the similarity between Emtriva and lamivudine, it is not unreasonable that these conclusions would apply to regimens containing Emtriva and efavirenz.

C.2 Review of Supportive Efficacy Studies-Controlled Studies

FTC-304 (ANRS 099, ALIZE,) is an ongoing open-label, randomized study comparing the efficacy and tolerability of maintaining a protease inhibitor (PI) containing regimen (maintenance) versus changing to the once-daily combination of Emtriva+ddI+EFV (switch) in patients with undetectable HIV RNA. The study has enrolled 355 patients, 177 in the maintenance arm and 178 in the switch arm. The study is to continue until all patients have completed 48-weeks of dosing. As of May 2002, 176 patients had at least 48 weeks of exposure in the switch arm. The study is being conducted by the French ANRS. The applicant did not submit efficacy data in this application. However, the ANRS presented results of the study at a recent international conference. According to the ANRS, 95% of patients in the switch group compared to 87% of maintenance patients had HIV RNA <50 c/mL at 48 weeks. Mean increase in CD4 cells and rates of treatment discontinuation were similar between treatment groups (Poster 551, 10th CROI, Boston, February 2003).

Comment: These results could not be confirmed since the data were not submitted as part of this NDA. If confirmed, they suggest that the Emtriva+ddI+EFV regimen is active and may represent an option for constructing a protease-inhibitor-sparing regimen.

ACTG-5015 is an ongoing study of the once-daily regimen of Emtriva+d4T+Kaletra® (lopinavir/ritonavir) in two age differentiated cohorts (13-30 years and ≥45 years) to evaluate the effect of age on immune reconstitution. The study is being conducted by the Division of AIDS of the NIH under US IND [redacted] The total duration of dosing is to be 48 weeks. As of September 2002, 91 patients had been enrolled, and 84 were on treatment. Through 24 weeks, the overall proportion of patients with HIV RNA ≤200 c/mL was reported to be 66% and ≤50 c/mL was 82%. No efficacy data was submitted.

Comment: Preliminary data suggest that the regimen is active, as would be expected from a Kaletra-based regimen. Since there is no control arm, it is not possible to determine the contribution of Emtriva to the 24-week efficacy results.

MKC-401 was a phase 3 study designed to evaluate the safety and efficacy of emivirine (MKC-442) a non-nucleoside reverse transcriptase inhibitor (NNRTI), compared to abacavir (ABC). In this study, 564 antiretroviral naïve patients with HIV RNA ≥1000 and <100,000 c/mL and CD4+ cell count >200 cells/mm^3 were randomized to receive MKC+Emtriva+d4T (n=376) or Emtriva+ABC+d4T (n=188). The study was designed as a 48-week equivalence study but was terminated early because of inferior antiviral activity in the MKC-442 arm. Since Emtriva was a component of both treatment arms, and the study was terminated early, no contribution of Emtriva to efficacy could be assessed.

C.3 Review of Supportive Efficacy Studies-Uncontrolled Studies

FTC-201 (ANRS-091/MONTANA) is an ongoing phase 2, open-label, non-randomized study evaluating the once-daily regimen of Emtriva+ddI+EFV. The study is being conducted in France. Forty treatment naive patients with HIV RNA ≥5000 c/mL, CD4+ cell count ≥100 cells/mm^3, and Karnofsky score ≥60% were enrolled. After 96 weeks of treatment, the proportion with HIV RNA reported to be ≤400 c/mL and ≤50 c/mL was 85% and 80%, respectively. The mean increase in CD4+ cell count from baseline is 259 cells/mm^3. The study is being conducted by the French ANRS. It remains ongoing and has been extended to 192 weeks (4 years).

FTC-350 is the rollover protocol for patients who completed study FTC-303 with HIV RNA <400 c/mL at 48 weeks. All patients were offered open-label access to Emtriva in addition to their current antiretroviral regimen until Emtriva becomes commercially available. A total of 289 patients entered study FTC-350. As of September 2002, 106 patients (37%) have discontinued the study for the following reasons: site closing (n=36), withdrawal of consent (n=28), virologic failure (n=15), adverse events (n=14), lost to follow-up (n=5), protocol violations (n=3), death (n=3), and non-compliance (n=2). The Kaplan-Meier probability of virologic failure, defined as HIV RNA >400 c/mL on two occasions 4 weeks apart, was reported to be 13.5%.

C.4 Review of Studies for Indications Not Included in the NDA

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D. Efficacy Conclusions

The results from two adequate and well-controlled studies and other comparative and non-comparative studies demonstrate that regimens containing Emtriva impart potent antiviral and

immunologic activity. However, no additional immunologic or virologic benefit was identified compared to 3TC when Emtriva® was used in either a first-line regimen or among patients who had virologic suppression on a 3TC-containing regimen. Compared to the regimen of d4T+ddI, the regimen containing Emtriva appeared more tolerable resulting in fewer discontinuations and less virologic failures; this finding is consistent with previous studies that reported similar findings for regimens containing 3TC.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Because patients in HIV studies receive multiple drugs that cause adverse events, it is often difficult to tease out the specific adverse events related to the drug of interest. In the case of Emtriva, however, the safety review benefits from the availability of adverse events from studies in which Emtriva is being or was administered as a monotherapy to patients with chronic HBV infection. In these studies, abdominal pain, asthenia, headache, malaise, pain, diarrhea, dyspepsia, nausea, arthralgia, dizziness, insomnia, paresthesia, increased cough, pharyngitis, rhinitis, pruritis, and rash were reported in ≥3% of patients.

Across the HIV-1 studies included in the NDA, the most common clinical adverse events included those listed above as occurring in HBV studies, as well as myalgia, bronchitis and sinusitis, depressive disorders, neuropathy, and vomiting. In the two comparative 3TC HIV studies, the types, frequency, and severity of adverse events were comparable between Emtriva arms and 3TC arms.

The Emtriva-based regimen used in study FTC-301A caused less adverse events than the d4T-based regimen. This finding is consistent with a significant body of evidence that the combination of d4T+ddI is more difficult to tolerate than 3TC-based regimens.

Grade 3 and 4 liver function abnormalities (elevated AST and ALT) occurred in approximately 5% of Emtriva-treated patients. The frequency was similar among patients in control groups, but led to more study medication discontinuations from Emtriva in study FTC-303. Excessive, but comparable hepatotoxicity occurred in study FTC-302, which was likely due to dose escalation of nevirapine (see **Adverse Events of Special Interest**).

Other nucleoside analogue related toxicities (e.g., pancreatitis, lactic acidosis, rash, and peripheral neuropathy) occurred with comparable frequency and severity compared to 3TC, but less than with d4T+ddI.

B. Description of Patient Exposure

Development of Emtriva® for treatment of adults with HIV infection has involved administration of the drug to over 2500 individuals: approximately 130 non-infected subjects in single and multiple dose studies and >2400 HIV-infected and HBV-infected patients in clinical trials. Long-term exposure/safety data was derived from approximately 1400 HIV infected adults who received Emtriva at the proposed marketing dose of 200 mg QD for ≥48 weeks. These data represent an estimated 3100 subject-years of exposure to Emtriva. These numbers represent patients who received at least one dose of medication.

Most patients enrolled in the controlled Emtriva clinical trials were male (66% versus 34%), with a mean age of 38 (range 18 to 70) years of age, and similar proportions of Caucasians and Africans, 42% and 45%, respectively. The Emtriva development program was international in scope with a significant number of patients being enrolled in clinical trials from Europe, South

America, and South Africa, which may have contributed to the ethnic distribution described herein.

C. Methods and Specific Findings of Safety Review

The safety review is based on review of phase 1 healthy volunteer, phase 2-3 adult controlled and uncontrolled HIV studies, and phase 2-3 HBV studies.

C.1. Deaths

Twenty deaths among patients treated with Emtriva were reported in the NDA (<1% of all patients): 19 in HIV studies and 1 in a HBV study.

All causes of deaths, regardless of relationship to Emtriva, included: hepatic failure (2), pneumonia (1), pulmonary edema (1), cerebral vascular accident (1), gastrointestinal bleeding due to renal failure (1), hyperkalemia due to renal failure (1), carcinoma of the liver (2), carcinoma (2), cardiac arrest due to a fire (1), lymphoma-like reaction (1), sudden cardiac death (1), accidental overdose (1), lactic acidosis (2), sepsis (1), meningitis (1), embolism (1), accidental injury (1). The relationship of Emtriva in the deaths due to hyperkalemia, the two cases of hepatic failure, the two cases lactic acidosis could not be completely ruled out.

In comparison, eight deaths were reported in patients not receiving Emtriva. The events in this population included: an apparent heart attack, ketosis, lymphoma-like reaction, meningitis, hepatic failure, sudden death possibly related to alcohol abuse, acute kidney failure, and an intentional overdose.

Comment: No specific patterns of toxicities leading to death were identified, and the causes were similar among patients not exposed to Emtriva. It was difficult to assess direct relationship to Emtriva because all patients were on multiple drugs. Pre-clinical testing did not identify specific events likely to cause death.

C.2. Serious and Severe Adverse Events

Serious adverse events (SAEs) were reported in 15% (236/1582) of patients treated with Emtriva in the HIV-1 studies. The most frequent SAEs reported included: hepatic-related events (hepatic failure, acute hepatitis, increased ALT and AST) observed most often in study FTC-302, accidental injury, infections, pneumonia, CNS events, rash events, lactic acidosis, gastrointestinal events (nausea, vomiting, diarrhea, and gastroenteritis), and abortion. The frequencies of these events were approximately 1-2% in each study. In trials in which there was a comparator arm, the types and frequencies of SAEs were generally similar between Emtriva and non-Emtriva containing arms.

Severe or life-threatening adverse events reported in clinical studies included elevated ALT and AST, rash events, increased amylase levels, CNS events, and headache. Again, the frequency of these events was comparable between Emtriva and control arms.

In HBV studies, SAEs were reported in approximately 12% of patients. The most common SAE was exacerbation of hepatitis B following cessation of therapy (which is important for labeling). Other SAEs included: headache, on-treatment hepatitis, threatened abortion, lung cancer, liver cancer, post liver biopsy pain and bleeding, nausea, vomiting, cerebral infarct, and accidental injury; each event occurring in <1% of cases.

C.3. Discontinuations due to Adverse Events

Approximately 9% of patients discontinued Emtriva® across all clinical trials. In controlled HIV studies, hepatic-related events (hepatic failure, hepatitis, abnormal liver function, unspecified hepatic toxicity, and increased AST/ALT) accounted for the majority of discontinuations. Other adverse events that led to discontinuations were diverse and infrequent, and included anemia possibly related to zidovudine, depression, anger, suicidal ideation, peripheral neuropathy. In uncontrolled studies, allergic reactions, lactic acidosis, liver function abnormalities, hepatic-related events, mylagia, pruritis, and rash appeared frequent reasons for discontinuation of treatment arms that contained Emtriva.

In studies FTC-302 and FTC-303 where Emtriva and 3TC were directly compared, more patients discontinued Emtriva for abnormal liver function (elevated AST and ALT), and increased amylase and lipase, than discontinued 3TC.

Discontinuations in the HBV studies were rare (2%), with the most common reasons being headache and digestive disorders.

C.4. General Clinical and Laboratory Adverse Events

The review of clinical and laboratory adverse events was conducted in the following manner:

1. The safety of Emtriva in Phase 1 studies was reviewed. The most common adverse events reported included headache, diarrhea, nausea, dizziness, drowsiness, and rhinitis.

2. In vivo Emtriva undergoes phosphorylation to 3TC monophosphate (which is subsequently converted to the active triphosphate). Therefore, it was reasonable to directly compare the types and frequencies of adverse events in the two studies in which Emtriva and 3TC were directly compared (studies FTC-302 and FTC-303). Selected events that occurred at ≥5% were compared between Emtriva and 3TC, and, where available, further compared to the most common clinical and laboratory adverse events listed in the Epivir® (3TC) label (see Table 7). For some events, the frequency was <5%, but they are included in the table to complete the comparison to historical data.

3. The types and frequencies of adverse events in study FTC-301A were reviewed to determine if there were any observable difference in the safety profiles of Emtriva and d4T (see Table 9).

4. Supportive controlled and uncontrolled HIV and HBV studies were reviewed to determine the frequency of events among patients taking Emtriva, and if any of these events had not previously been observed for 3TC.

C.4.1 General Clinical Adverse Events

Table 7 presents a comparison of adverse events (regardless of severity or relationship to drug) reported in the two 3TC comparative studies (FTC-302 and FTC-303), with a comparison to available historical 3TC adverse event rates as listed in the currently approved Epivir® label.

Table 7. Adverse events occurring in >5% of patients in studies in studies FTC 303 and FTC-302 with comparison to historical rates.

	FTC-303		FTC-302		3TC Historical*
Adverse event	Emtriva 200 mg QD (n=294)	Epivir 150 mg BID (n=146)	Emtriva 200 mg QD (n=234)	Epivir 150 mg BID (n=234)	
Body as a whole					
Headache	13%	6%	35%	38%	5%
Pain	15%	12%	16%	15%	
Asthenia	16%	10%	15%	14%	
Fever or chills	9%	6%	4%	7%	10%
Digestive					
Abdominal pain	8%	11%	19%	20%	9%
Nausea	18%	12%	22%	21%	33%
Vomiting	9%	7%	17%	16%	13%
Diarrhea	23%	18%	22%	27%	18%
Anorexia	5%	2%	6%	6%	10%
Dyspepsia	4%	5%	6%	6%	5%
Hemic and Lymphatic					
Lymphadeno-pathy	11%	6%	10%	11%	
Nervous system					
Neuropathy	4%	3%	6%	5%	12%
Insomnia	7%	3%	3%	5%	
Dizziness	4%	5%	7%	14%	11%
Depressive disorders	6%	10%	4%	7%	10% 9%
Respiratory					
Rhinitis	18%	12%	11%	10%	20%
Increased cough	14%	11%	13%	13%	18%
Pharyngitis	11%	12%	15%	15%	
Bronchitis	5%	8%	8%	12%	
Sinusitis	6%	7%	4%	4%	
Skin					
Rash event[1]	17%	14%	23/33%	21/29%	9%
Herpes simplex	6%	4%	5%	6%	
Metabolic					
Lipodystrophy	9%	6%	0	0	
Musculoskeletal					
Myalgia	4%	4%	6%	4%	8%
Arthralgia	3%	4%	5%	4%	5%

Source: NDA reports for studies FTC-302 (Table 31, Volume 5.21) and FTC-303 (Table 21, Volume 5.3).
1. Rash event includes rash, pruritis, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.
* From the Epivir® (3TC) label dated August 2001.

Approximately 16% of patients in each treatment arm of study FTC-302 required a dose modification or interruption of the study regimen. The reasons for dose modification or interruption were similar between treatment arms with the most common being headache, nausea, vomiting, rash, and increased AST and ALT.

Table 8 presents the most frequently (>5%) reported treatment-emergent adverse events reported in study FTC-301A, all grades, and regardless of relationship to study drug.

Table 8. Clinical Adverse Events in Study FTC-301A

Adverse Event	Emtriva® (n=286)	Zerit® (n=285)
Body as a Whole		
Headache	22%	25%
Pain	18%	20%
Asthenia	12%	17%
Fever or chills	7%	8%
Digestive		
Diarrhea	23%	32%
Abdominal pain	14%	17%
Nausea	13%	23%
Vomiting	9%	12%
Dyspesia	8%	12%
Anorexia	3%	6%
Musculoskeletal		
Arthralgia	5%	6%
Myalgia	6%	3%
Nervous system		
Dizziness	25%	26%
Insomnia and other sleep disorders	16%	21%
Abnormal dreams	11%	19%
Depressive disorders	9%	13%
Neuropathy	4%	13%
Respiratory		
Pharyngitis	12%	10%
Bronchitis	13%	16%
Rhinitis	14%	10%
Increased cough	14%	8%
Sinusitis	8%	10%
Skin		
Rash event[1]	30%	33%
Herpes simplex	12%	9%

Source: NDA report for study FTC-301A (Table 22, Volume 5.2). Safety update submitted December 27, 2002.
1. Rash event includes rash, pruritis, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

The combination of d4T+ddI has an established toxicity profile that is well characterized and is associated with poor tolerability of the regimen. Expected adverse events related to ddI+d4T include peripheral neuropathy, asthenia, diarrhea, nausea, pancreatitis, lactic acidosis, hepatic steatosis and hepatic failure. In study FTC-301A, these events led to the higher rate of discontinuations from the d4T+ddI arm, and likely led to the efficacy difference between treatment arms.

Insomnia, sleep disorders, and abnormal dreams have occasionally been reported among patients receiving 3TC, and were occasionally reported in patients taking Emtriva. In study FTC-301A, all patients received efavirenz, which is known to frequently cause these types of events. Therefore, since the frequency of these events were low in studies FTC-302 and FTC-303 in

which very few patients received efavirenz, it is likely efavirenz was the reason for the higher frequency observed in study FTC-301A.

In a single dose study (study FTC-103), Emtriva increased the $AUC_{0-\infty}$ and C_{max} of ZDV by 26% and 66%, respectively. In study FTC-303, approximately 150 patients received concomitant Emtriva and ZDV for up to 48 weeks. The frequency and severity of anemia, the primary dose limiting toxicity of ZDV, was comparable between groups who received ZDV with Emtriva or 3TC. Thus, the increases in certain ZDV pharmacokinetic parameters did not appear to impact its clinical safety.

C.4.2 Laboratory Abnormalities

A comparison of laboratory abnormalities was also conducted. There were no observable differences between Emtriva and 3TC with respect to severe (Grade 3 or 4) laboratory abnormalities. Comparisons to historical 3TC rates were not included because there were very few laboratory events listed in the 3TC label and the grading system using in the 3TC label was different from the system used in the FTC studies.

Between 30-40% of patients in studies FTC-301A, FTC-302, and FTC-303 experienced Grade 3 or 4 laboratory abnormalities (see Tables 9 and 10).

Table 9. Laboratory Abnormalities in Studies FTC-303 and FTC-302

	FTC-303		FTC-302	
	Emtriva (n=294)	Epivir (n=146)	Emtriva (n=234)	Epivir (n=234)
% with Grade 3 or 4 abnormality	40%	38%	31%	31%
AST				
All Grades	28%	27%	46%	49%
Grade 3-4 (>5 x ULN)	3%	1%	12%	10%
ALT				
All Grades	26%	25%	48%	49%
Grade 3-4 (>5 x ULN)	2%	1%	13%	15%
Bilirubin				
All Grades	17%	19%	6%	6%
Grade 3-4 (>5 x ULN)	1%	2%	2%	3%
Serum lipase				
All Grades	1%	2%	6%	3%
Grade 3-4 (>2 x ULN)	1%	1%	2%	1%
Serum amylase				
All Grades	14%	16%	19%	22%
Grade 3-4 (>2 x ULN)	2%	2%	2%	4%
Creatine kinase				
All Grades	41%	52%	59%	53%
Grade 3-4 (> 4 x ULN)	11%	14%	11%	13%
Glucose				
All Grades	52%	54%	53%	60%
Grade 3-4 (>250 mg/dL)	3%	3%	4%	<1%
Triglycerides				
All Grades	22%	28%	4%	4%
Grade 3-4 (>750 mg/dL)	10%	8%	1%	1%
Neutrophils				
All Grades	25%	14%	35%	31%
Grade 3-4 ($<750/mm^3$)	5%	3%	3%	3%

ULN= Upper Limit of Normal

Source: NDA reports for studies FTC-302 (Table 35, Volume 5.21) and FTC-303 (Table 27, Volume 5.3).

Table 10. Laboratory Abnormalities in Study FTC-301A

	Emtriva (n=286)	Zerit (n=285)
% with Grade 3 or 4 abnormality	29%	36%
AST		
-All Grades	27%	51%
-Grade 3-4 (>5 x ULN)	6%	9%
ALT		
-All Grades	27%	51%
-Grade 3-4 (>5 x ULN)	5%	6%
Bilirubin		
-All Grades	2%	5%
-Grade 3-4 (>2 x ULN)	<1%	<1%
Creatine kinase		
-All Grades	40%	42%
-Grade 3-4 (>4 x ULN)	10%	10%
Serum lipase		
-All Grades	4%	4%
-Grade 3-4 (>2 x ULN)	1%	2%
Serum amylase		
-All Grades	36%	46%
-Grade 3-4 (>2 x ULN)	5%	10%
Pancreatic amylase		
-All Grades	4%	7%
-Grade 3-4 (>2 X ULN)	<1%	1%
Glucose		
-All Grades	42%	42%
-Grade 3-4 (>250 mg/dL)	2%	3%
Triglycerides		
-All Grades	20%	18%
-Grade 3-4 (>750 mg/dL)	9%	6%
Neutrophils		
-All Grades	25%	22%
-Grade 3-4 (<750/mm^3)	5%	7%

ULN= Upper Limit of Normal
Source: NDA report for study FTC-301A (Table 33, Volume 5.9).

Although more patients discontinued Emtriva, the overall frequency of AST, ALT, and bilirubin elevations were comparable between the Emtriva arms in studies FTC-301A and FTC-303. The LFT abnormalities in study FTC-302 were associated with higher rates of clinical hepatotoxicity, which was likely due to the use of nevirapine in the study (see below). Compared to d4T, the frequency of Grade 3 or 4 LFT abnormalities was similar.

The longer duration of therapy with protease inhibitors in study FTC-303 may have led to the higher rates of triglyceride elevations.

Review of data from other controlled and uncontrolled supportive HIV studies yielded no new specific safety concerns.

In HBV studies, Emtriva is being or was administered as monotherapy, thus providing a reasonably good assessment of events directly related to Emtriva. The most common adverse events include headache, flu syndrome, gastrointestinal events (diarrhea and abdominal pain)

malaise, asthenia, and rash. Abnormalities of liver function, specifically elevations in transaminase levels, occurred in 6-10% of patients. Of note, a number of patients experienced flares of liver function (i.e., Grade 3-4 elevations of AST and ALT) following cessation of Emtriva therapy. This phenomenon has been described in patient treated with 3TC and is thought to be related to exacerbation of hepatitis following removal of anti-HBV drug pressure.

Comment: The types and frequencies of adverse events observed in HBV studies were generally comparable to those observed in the HIV studies.

C.5. Adverse Events of Special Interest

Hepatotoxicity, lactic acidosis/hyperlactidemia, pancreatitis, and rash are well-described adverse events associated with nucleoside analogues used for treatment of HIV, and may be a possible consequence of drug-induced mitochondrial toxicity. Pre-clinical testing suggested that Emtriva® did not have strong affinity for mitochondrial enzymes. However, since Emtriva is a nucleoside analogue, it was prudent that these events be reviewed and discussed to ensure that a potential signal would not be missed.

Emtriva was administered with at least 2 other antiretroviral agents, which also cause adverse events and could confound an accurate assessment of events directly related to Emtriva. Emtriva is being administered as a single agent compared to placebo to patients with chronic HBV infection. Therefore, these patients provide a less biased opportunity to assess Emtriva-related events.

Some HIV-infected women become pregnant in the clinical trials. Although the studies precluded enrollment of pregnant women, required women of childbearing age to practice birth control, and monitored for the occurrence of pregnancy, some women did become pregnant. According to the applicant, antiretroviral therapy was interrupted in all cases of pregnancy. Pregnancy is not a specific contraindication to antiretroviral therapy, and preclinical data suggested that Emtriva did not pose an undue risk to the developing fetus. Therefore, the occurrence and outcomes of pregnancies that occurred in clinical studies were evaluated in an attempt to determine if the preclinical data was, in fact, predictive of clinical outcomes.

An interesting finding of skin discoloration occurring more frequently in non-Caucasians was identified during review of the NDA.

C.5.1 Hepatotoxicity

Early in the conduct of study FTC-302, significant hepatotoxicity, defined grade 3 and 4 elevations of liver function tests (bilirubin, alkaline phosphastase, ALT, and AST) was reported, and there were three deaths secondary to liver failure. Although hepatotoxicity has been reported to occur with all NRTI (there is hepatotoxicity-related class labeling), the Division was concerned that FTC's additional flouride residue may have caused the hepatotoxicity to be more severe, as the pattern was similar to that observed with another fluorinated nucleoside analogue: FIAU. FIAU was being investigated for the treatment of HBV in HIV-1 infected patients. During clinical trials, significant numbers of patients experienced moderate AST and ALT

elevations, and two patients experienced fulminant hepatic failure that required liver transplantation; deaths due to liver failure were also reported. Development of FIAU was subsequently discontinued due to these events.

In study FTC-302, patients with baseline HIV RNA <100,000 c/mL received nevirapine (an NNRTI) and d4T (an NRTI) as unblinded background antiretroviral therapy. Nevirapine is administered as one 200 mg tablet once-daily for 14 days and then one 200 mg tablet twice daily. All patients with HIV RNA >100,000 c/mL received efavirenz instead of nevirapine.

A total of 66 patients (29 Emtriva and 37 3TC) experienced at least one Grade 3 or 4 hepatotoxic event during the study, all of which occurred among patients who received nevirapine. The majority of patients also experienced signs/symptoms of hepatitis (nausea, vomiting, rash, jaundice, liver or abdominal tenderness). All cases occurred in patients receiving nevirapine.

Review of demographic characteristics of patients experiencing hepatotoxicity revealed that they were more often female (46 versus 20) with a mean baseline CD4 cell count of 444 cells/mm^3 (range 177-930 cells/mm^3). Four patients were HbsAg positive and two had serologic evidence of hepatitis C virus infection at screening.

There was a pattern of hepatotoxicity observed in FTC-302. Typically patients began to experience clinical signs and symptoms shortly after escalation of their nevirapine dose from 200 mg once daily to 200 mg twice daily during week 2 of the study. Then, at the next scheduled visit (approximately study week 4) the patient was found to have clinical signs and symptoms of hepatotoxicity. Of the 66 patients, 18 were treated through the hepatotoxicity without sequelae and 17 had medications temporarily interrupted and reintroduced after toxicity resolved. Twenty-one patients (32%) permanently discontinued study medications. Eight patients were switched from nevirapine to efavirenz after their toxicity resolved.

Two patients died, one in each treatment group. Both were black females. Both experienced Grade 4 ALT and AST elevations within 4 weeks of study entry (two weeks following escalation of nevirapine from once to twice daily, and both died within one week of discontinuation of study medication.

In summary, the hepatotoxicity observed in study FTC-302 followed closely the pattern (following escalation of nevirapine from 200 mg once daily to 200 mg twice daily) and the at-risk population (females) described in the nevirapine labeling.

An additional death due to hepatotoxicity was reported in a 22-year old black female who received Emtriva+d4T+MKC-442 (a NNRTI) in study MKC-401. On study day 14, the dose of MKC-442 was increased from 1000 mg/day to 1500 mg/day. On day 23 she was noted to have a rash, on day 29 she had Grade 4 elevations of her AST and ALT, on day 57 she was hospitalized, and on day 65 she died as a result of hepatitis.

In studies FTC-301A and FTC-303, approximately 9% of patients were co-infected with HBV or HCV. In general, the frequency of Grade 3 and 4 transaminitis in the Emtriva arms was similar to the comparator arms.

In study FTC-301A, Emtriva-treated patients experienced seven hepatotoxic events: hepatomegaly (3), hepatitis (1), reactivation of hepatitis B (2), and jaundice (1).

In HBV trials, on treatment transaminitis were reported in 15% of patients treated with Emtriva; approximately 7% of these events were considered Grade 3 or 4. More commonly, however, patients experienced post-treatment exacerbation of hepatitis B days to weeks following cessation of treatment as evidenced by significant transaminitis and hyperbilirubinemia.

C.5.2. Pancreatitis

Emtriva, like 3TC, was not expected to cause significant cases of pancreatitis. Only six cases of pancreatitis were reported in the over 2000 patients contained in the safety database who were treated with Emtriva; five were adults and one was a pediatric patient. None died, and four were receiving concomitant d4T at the time pancreatitis was diagnosed.

C.5.3. Symptomatic hyperlactatemia/lactic acidosis

In studies FTC-301A, FTC-302 and FTC-303, there were no cases of symptomatic hyperlactatemia/lactic acidosis reported in the Emtriva arms. In study FTC-301A, there were seven patients who experienced symptomatic hyperlactatemia/lactic acidosis in the d4T arm; two also had hepatic steatosis, one also had pancreatitis, and one had peripheral neuropathy. Two of the cases were judged to be life threatening, and one was considered severe; two of these patients had resolution following study drug discontinuation, and for one the outcome is unknown because he was lost to follow-up.

C.5.4. Peripheral Neuropathy

Peripheral neuropathy was reported in <10% of Emtriva patients, which was comparable to 3TC, but lower than in patients in study FTC-301A who received d4T+ddI. The majority of cases were mild to moderate, no cases were life-threatening, and no patients discontinued Emtriva due to peripheral neuropathy.

C.5.6. Rash

Nucleoside analogues are known to cause rashes. The applicant defined a "rash event" as allergic reaction, angioedema, erythema multiforme, maculopapular rash, pruritis, pustular rash, urticaria, or vesiculobullous rash. A rash event was reported by approximately 27% of patients who received Emtriva. The majority of rash events were mild to moderate in severity. There were 2 cases of Stevens-Johnson syndrome reported in FTC-302, both patients were receiving Emtriva and nevirapine.

Overall, rash events were reported with similar frequency between patients treated with Emtriva compared to 3TC and d4T (see Tables 7 and 8, above).

The majority of significant rash events occurred in study FTC-302, and appeared temporally related to the increase of nevirapine from 200 mg QD to 200 mg BID.

Rash and pruritis were the most commonly reported skin-related events in the ongoing HBV studies; the frequency was approximately 5% for both.

C.5.7. Pregnancy

Female patients of childbearing potential were required to have evidence of a negative pregnancy test prior to entry. In addition, they were instructed to practice birth control, and were to undergo pregnancy testing every three months. Despite these efforts, 53 women exposed to Emtriva became pregnant. Twenty-nine were terminated by medical abortion, six spontaneous abortions were reported, and there were 19 live births.

At the time pregnancy was reported, study medications were interrupted. Five women were allowed to restart therapy if they had been off study medications for less than 30 days and if they were beyond the first trimester; all five gave birth to healthy babies.

C.5.8 Skin Discoloration

Skin discoloration was reported to occur in 13% (176/1348) of patients in the applicant's largest HIV studies: FTC-301A, FTC-302, FTC-303, and MKC-401. The skin discoloration was described as hyperpigmentation on the palms and soles, and it predominantly occurred in black patients. In the majority of cases, investigators assessed the severity as mild, and no patients discontinued HIV studies due to this event. However, two patients in a HBV study (FTCB-301) discontinued due to skin discoloration.

The Division of Dermatologic and Dental Drug Products (HFD-540) was consulted for an opinion on the potential clinical significance of skin discoloration, and for recommendations for labeling and postmarketing studies.

The Dermatology reviewer found that hyperpigmentation has been noted in patients with HIV infection and is well documented in the literature. Many of the cases may be associated with anti-retroviral therapy, and/or due to concomitant medications such as Bactrim. For example, proliferation or accentuation of palmar/plantar hyperpigmented macules due to zidoviudine has been noted in one publication (Bendick, Rasokat, and Steigleder, Arch. Dermatol., 1989). This type of drug induced hyperpigmentation is especially common in African-American patients. The hyperpigmentation has been described as being more prominent in the sun-exposed areas of the skin (e.g. greater darkening of the face than the covered torso. Mucosal and non-sun-exposed surfaces have also been noted to be involved. Accentuation of palmar/plantar and non-palmar/plantar hyperpigmented macules can be seen in patients on various chemotherapeutic agents, such as doxorubicin, adriamycin, bleomycin.

The differential diagnosis of new onset palmar/plantar hyperpigmented macules includes secondary syphilis. This should be given high consideration due to the population being studied (HIV positive patients). Long-standing, single hyperpigmented macules on the palms and soles

in African Americans that are changing (e.g., becoming more accentuated) should give rise to concern about acral lentiginous melanoma. However, this could be ruled out by examination of the lesions by a dermatologist and from history.

In summary, the mechanism and clinical significance of skin discoloration remains unknown, and the labeling will include this information. A post-marketing commitment to evaluate further the nature of these lesions will be obtained. Subjects should have pigmented lesions further assessed. Additional assessment should include screening for RPR and evaluation of concomitant medications. Close-up photographs could help in the documentation and evaluation of these lesions, and biopsies should only be obtained when clinically indicated.

D. Adequacy of Safety Testing

The safety database is robust and contains short and long-term exposure data on >2000 HIV-1-infected and >500 HBV-infected patients exposed to Emtriva® in clinical studies.

E. Summary of Critical Safety Findings and Limitations of Data

Emtriva® exhibited a clinical and laboratory adverse event profile comparable to 3TC. Adverse events occurred with similar frequency in patients treated with Emtriva and 3TC, and occurred with generally less frequency than reported in historical data.

The most common adverse clinical events and laboratory abnormalities include: headache, pain. asthenia, fever/chills, abdominal pain, nausea, vomiting, diarrhea, rhinitis, increased cough, pharyngitis, rash, and increased AST and ALT; these events will be listed in the label.

The safety data reviewed in this NDA demonstrates that Emtriva and 3TC have a comparable safety profile. Compared to d4T, there was a clear difference in adverse events with d4T-treated patients experiencing more gastrointestinal, hepatic, and peripheral neurological events; events that have been well characterized among patients receiving d4T alone and in combination with ddI. These toxicities have led to recommendations that use of d4T+ddI be curtailed, at least as a first-line NRTI regimen.

When adverse events reported in patients treated with Emtriva in studies FTC-301A, FTC-302 and FTC-303 were compared, the rates were generally similar across all Emtriva-containing arms.

The excess frequency of rash (which occurred similarly in both arms) and hepatotoxicity in study FTC-302 was likely due to nevirapine.

The concern that hepatoxicity observed in patients treated with Emtriva was more severe than that observed with other NRTIs was not borne out. Although several patients experienced significant hepatotoxicity, the frequency and severity were similar amongst patients treated with Emtriva and other NRTIs. There was no hepatic toxicity noted in preclinical toxicity studies. The Emtriva label will, however, contain the same class warning related to hepatotoxicity that is included in other nucleoside labels. In addition, there is a concern, as with other medications

with activity against both HIV and HBV that post treatment exacerbation of hepatitis may occur once therapy is withdrawn. There were cases of this phenomena identified in the NDA. Therefore, the label will include a warning to clinicians about this potential risk.

With respect to other nucleoside analogue-related toxicities (rash, pancreatitis, hyperlactatemia/lactic acidosis, and peripheral neuropathy), the frequency and severity were comparable to 3TC. Pancreatitis, hyperlactatemia/lactic acidosis, and peripheral neuropathy occurred more often among patients who received d4T+ddI, as expected.

Review of the outcomes of pregnancies reported among women exposed to Emtriva did not suggest an increased risk to the health of the woman or the developing fetus. However, adequate and well-controlled studies have not been conducted, so it is unknown if Emtriva may have contributed to the spontaneous abortions. Therefore, given the preclinical and clinical data reviewed herein, Emtriva will be labeled Category B.

The safety data from study FTC-302 was reviewed in order to create a more robust database and provide additional patients for comparisons. No new Emtriva-related adverse events were identified, and as mentioned above, the frequency and severity of adverse events between Emtriva and 3TC were generally comparable. However, because of the problems with its conduct, because it remains on Clinical Hold, and because there were no new findings with regard to Emtriva, the labeling will not contain any reference to study FTC-302.

VIII. Dosing, Regimen, and Administration Issues

The adult dose of Emtriva is one-200 mg capsule daily administered without regard to food. The dose is based on the results of 2 phase 1 studies (FTC-101 and FTC-102) in which escalating doses of FTC were administered for 14 days. Early in development, the Division expressed concerns about the utility of the database from the phase 1 studies as the basis for selection of the dose for phase 3 studies and potential risks to the applicant associated with such a selection. Concerns were raised about the small number of subjects enrolled, the limited duration of dosing (it was not possible to extend dosing beyond 2 weeks for fear of resistance), and whether the data on reductions in HIV RNA demonstrated meaningful differences among the doses studied in FTC-101 and FTC-102. It was suggested that additional dose finding studies be conducted that the clinical trials be modified to include additional doses of FTC for comparisons. The sponsor was encouraged to propose additional dose finding studies, taking into account trial design issues, practicality, and any ethical considerations associated with the conduct of such trials. The applicant chose to initiate all clinical trials using the 200 mg dose. In summary, the 200 mg QD dose appears active, and although it may not be optimal, provides reasonable antiviral benefit and safety margins.

Dosing for patients with renal insufficiency (CrCl <50 mg/mL) will be every 48-96 hour based on CrCl.

IX. Use in Special Populations

A. Evaluation of Gender Effects Analyses and Adequacy of Investigation

Gender

Males and females accounted for 58% and 42% of HIV-1 clinical trial enrollees. There did not appear to be any significant safety differences between males and females. The types of adverse events were similar. Males reported headache, constipation, pruritis, rash, and skin discoloration more frequently and females reported urogenital events more often. The frequency and severity of other adverse events were comparable.

With respect to efficacy outcomes, it appeared that males had better virologic responses than females. In study FTC-303 this may have been due to higher discontinuations among females due to adverse events, and in study FTC-301A only 15% of study participants were female.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Ethnicity/Race

Approximately 72% of patients enrolled in Emtriva HIV-1 studies were Caucasian.

Racial or ethnic differences did not appear to impact overall response to Emtriva treatment.

Non-Caucasians experienced higher rates of headache, increased AST and ALT, dizziness and skin discoloration. Conversely, Caucasians reported more insomnia and elevated triglyceride levels. The higher rates of increased AST and ALT among non-Caucasians was likely influenced by the overall high frequency of these events in study FTC-302 where >95% of the study population was non-Caucasian. The primarily Caucasian population in study FTC-303, the majority of whom were receiving protease inhibitors, appeared to account for the higher frequency of elevated triglycerides.

Age

In study FTC-301A, the median age of patients was 31 years compared to 41 years in study FTC-303. In general, older patients had lower virologic responses and higher LOVR compared to younger patients.

Patients ≥65 years of age accounted for <1% of HIV-1 trial participants; thus, it was not possible to reach any conclusions about safety or efficacy in this subgroup. Also, there are insufficient pharmacokinetic data in this age group. Although the numbers of elderly patients with HIV-1 infection is overall relatively small, there do not appear from preclinical or clinical studies, any overt contraindications to using Emtriva in this age group. Caution should be exercised, however, in elderly patients who often have decreased renal function; Emtriva should not be administered to patients with a CrCl <50 mg/mL. Additional safety, pharmacokinetic, and efficacy data in this population would be helpful; the applicant will be asked to supply these data as a Phase 4 commitment.

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X. Conclusions and Recommendations

A. Conclusions

The efficacy data demonstrate that antiretroviral drug regimens including Emtriva® plus two other agents are virologically and immunologically active and produce activity, as measured by suppression of HIV-1 RNA and increases in CD4 cell counts, generally comparable to other triple drug regimens. Thus, Emtriva administered once daily, as part of a multiple drug regimen, represents an additional option for patients who might benefit from a once daily antiretroviral regimen.

Despite *in vitro* data suggesting greater activity of Emtriva compared to 3TC, there was no immunologic or antiviral advantage in favor of Emtriva over 3TC demonstrated in two clinical studies. At the time the phase 3 studies were initiated, Epivir® was approved only for twice daily administration. Since then, Epivir has been approved for once-daily administration. Therefore, any potential advantage for Emtriva with respect to compliance due to once daily frequency of dosing is limited. A regimen that contains Emtriva appear better tolerated than regimens containing d4T+ddI; a conclusion that has also been reached for regimens containing 3TC.

In HIV trials adverse event data were collected on the entire study drug regimen, which can make it difficult to specify an individual study drug as being related to a particular adverse event. Based on the review of the safety database, Emtriva was generally well tolerated with a safety profile comparable to Epivir. The most common adverse events related to Emtriva included: headache, nausea, vomiting, diarrhea, rash, skin discoloration (primarily amongst non-Caucasians which will be described in the label), and elevated ALT and AST.

Specific nucleoside-related toxicities (i.e., hepatotoxicity, lactic acidosis, rash) also occurred with comparable frequency and severity as 3TC. However, more patients discontinued from the d4T+ddI arm of FTC-301A due to pancreatitis and peripheral neuropathy, which likely led to the differential efficacy results.

Post treatment exacerbation of hepatitis was noted in HBV studies. Although FTC will not be indicated for HBV, a number of HIV infected patients are co-infected with HBV. Thus, some patients with HBV may actually receive FTC. In these cases, there is a potential concern that should a patient discontinue FTC (as anti-HIV therapy) they could experience an exacerbation of hepatitis. The labeling will carry a WARNING to alert clinicians to this possibility.

Resistance to Emtriva emerges rapidly both *in vitro* by a few passages of the virus in cells and *in vivo* by a few weeks of monotherapy. The pattern of resistance is similar to lamivudine and is typically manifested by a change at codon 184 of the reverse transcriptase with methionine being substituted with valine or isolucene (M184V/I). The need for clinicians to assess susceptibility to Emtriva in treatment experienced will be highlighted in the label, as these patients may be less likely to respond to Emtriva if they have previously received 3TC and harbor the M184V/I mutation.

B. Recommendations

Based on the review of the clinical safety and efficacy data submitted in NDA 21-500, this reviewer recommends the Emtriva® application be approved.

TMO review

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/s/

Russell Fleischer
7/2/03 12:34:02 PM
MEDICAL OFFICER

Jeffrey Murray
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