CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-500

Medical Review(s)

NDA 21-500
Emtriva® (emtricitabine) Capsules

For: Treatment of HIV-1 Infection in Adults

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I. Recommendations

A. Recommendation on Approvability

Based on review of the materials submitted in this NDA, it is recommended that the application be approved.

This recommendation is based on a thorough review of a robust safety and efficacy database derived from multiple large clinical trials conducted in HIV infected patients. The efficacy data demonstrate that antiretroviral drug regimens including Emtriva plus two other agents are active and produce antiviral and immunologic activity, as measured by suppression of HIV-1 RNA and increases in CD4 cell counts, comparable to other triple drug regimens. Thus, Emtriva administered once daily represents an additional option for patients who might benefit from a once daily antiretroviral regimen.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

A patient package insert for Emtriva® will be distributed with each prescription.

The applicant has committed to further investigate the mechanism and clinical significance of the adverse event skin discoloration.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Emtriva® (emtricitabine, FTC, nee Coviracil®) is an antiviral agent intended for oral administration to treat HIV-1 in patients >18 years of age. The clinical development program for this indication consisted of two pivotal and 5 supportive studies. Throughout development more than 2500 HIV-1 infected patients have been exposed to Emtriva for more than 48 weeks at the dose proposed for approval: 200 mg QD. In addition, Emtriva has been investigated in pediatric patients with HIV-1 infection and in adults with chronic hepatitis B virus (HBV) infection.

B. Efficacy

Emtriva® is a cytosine NRTI. Emtricitabine has the same chemical structure as lamivudine (3TC) except for a fluoride residue at position 5 on the pyrimidine ring. In cells, emtricitabine is phosphorylated to a 5'-triphosphate (FTC-TP) much the same as 3TC is phosphorylated to its active triphosphate. Since Emtriva is structurally similar to 3TC it was expected to produce similar antiviral activity and safety profile as 3TC.

The antiviral and immunologic activity of Emtriva was investigated in two large controlled studies (FTC-301A and FTC-303) and supported by several other controlled and uncontrolled studies. Across these studies, the regimens containing Emtriva were active.

Comparison to Epivir® (3TC, lamivudine [GlaxoSmithKline])

Emtriva® was directly compared to 3TC in two studies. In study FTC-303, patients who had evidence of viral suppression (HIV RNA <400 c/mL) on a 3TC-containing regimen were randomized 2:1 to switch to Emtriva or remain on 3TC. At the end of the 48-week dosing period, the proportion of patients with continued suppression of HIV RNA to <400 c/mL (the primary endpoint) was 73% among patients who switched to Emtriva compared to 82% who remained on 3TC (p=0.05 for the difference). Similarly, a higher proportion of patients who remained on 3TC experienced suppression of their HIV RNA to <50 c/mL (75% versus 68%), and had corresponding increases in CD4 cell counts (+61 cells/mm^3 versus +29 cells/mm^3). The efficacy difference appears to have been driven by the higher rate of discontinuations from the Emtriva arm due to adverse events. Since this was an open label study and clinicians and their patients knew their treatment assignment, it is possible that they were sensitized to the occurrence of new adverse events leading to asymmetrical discontinuations from Emtriva.

FTC-302 was to serve as a pivotal study but was terminated early by the South African regulatory authorities for poor GCP adherence and multiple ethical digressions, for these reasons, DAVDP placed the study on CLINICAL HOLD. In this study, once daily Emtriva was compared directly to twice-daily 3TC among antiretroviral therapy-naïve patients. Due to communications problems between the applicant and the South Africans, the study continued and 48-week blinded data became available. Although not reviewed in detail, the overall results demonstrated less efficacy among patients treated with Emtriva than those who received 3TC. Specifically, the proportion of patients with HIV RNA <400 c/mL and <50 c/mL were 64% and 60% in the Emtriva arm and 71% and 64% in the 3TC arm, respectively. Thus, FTC-302 can be considered supportive of the overall conclusions of study FTC-303 in that there are no apparent efficacy advantages in favor of Emtriva over 3TC.

Comparison to Zerit® (d4T, stavudine [Bristol-Myers Squibb])

In study FTC-301A Emtriva® was directly compared to d4T on a background of didanosine (ddI) and efavirenz (EFV) in treatment naïve patients.

The regimen containing Emtriva produced better antiviral activity and safety than d4T, however, this may be related to the poor tolerability of d4T when used in combination with ddI. Similar results were observed when the combination of 3TC and zidovudine was compared to a regimen containing d4T+ddI in ACTG 384, and adds to the database of studies suggesting that the combination of d4T+ddI is no longer a preferred first line nucleoside backbone due to excessive toxicities. Further, given the results of studies FTC-302 and FTC-303, it is highly likely that if 3TC had been used in this study rather than Emtriva, similar results would have been obtained.

Summary of Efficacy

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 now moot. Regimens containing Emtriva either with or without d4T appear likely to be better tolerated than regimens containing d4T+ddI; a conclusion that has also been reached for regimens containing 3TC.

Finally, multi-drug regimens containing Emtriva were demonstrated to be active, thus, Emtriva represents an additional once-daily NRTI choice for clinicians and patients to consider when constructing a primary anti-HIV regimen. Emtriva unlikely has a role in patients who are doing well on a 3TC containing regimen. There are no data in more advanced patients (e.g., patients who have failed previous NRTI therapy) upon which to make a recommendation for use.

C. Safety

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. However, in this case, Emtriva® has been administered as a monotherapy to patients with chronic hepatitis B virus (HBV) infection; thus, it was possible to identify certain adverse events related to Emtriva, and to assess their frequency and severity in the HIV studies.

Based on the review of the safety database, it can be concluded that 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), 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).

D. Dosing

The proposed Emtriva® dose is one-200 mg capsule administered once daily (QD). This dose was selected based on the results of 2 two-week monotherapy comparisons to 3TC. The

applicant concluded that this dose maintains antiviral concentrations above the IC_{90} for a significant portion of the dosing interval. Although this was potentially not the optimal dose of Emtriva, it is an active dose based on exposure-response relationships.

Emtriva is 4% protein bound; therefore, interactions with drugs that are protein mediated are unlikely. Emtriva exposure is increased 4-6.5 fold following ingestion of a full high fat high calorie meal; therefore, patients will be instructed to take Emtriva with a meal.

Patients with renal insufficiency can be dosed with Emtriva on an every 48-96 hour schedule (see **Special Populations: Renal Impairment**).

E. Special Populations

Ethnicity/Race

Approximately 72% of patients enrolled in Emtriva HIV-1 studies were Caucasian. There was no ethnicity-related differences in clinical outcomes between patients who received Emtriva or 3TC.

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 ALT and AST 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, and receiving nevirapine. The primarily Caucasian population in study FTC-303, the majority of who were receiving protease inhibitors, appeared to account for the higher overall frequency of elevated triglycerides.

No specific dosing modifications based on race/ethnicity are recommended in the labeling.

Gender

Males and females accounted for 58% and 42% of HIV-1 clinical trial enrollees, respectively. With respect to efficacy outcomes, in general females experienced more virologic failures compared to males. This may have been attributable to higher discontinuations among females due to adverse events from study FTC-303, and a low proportion of females (15%) in study FTC-301A. There was no gender difference between Emtriva and 3TC, overall.

The types of adverse events reported by males and females were similar, although more females discontinued from study FTC-303 because of adverse events. Males reported headache, constipation, pruritis, rash, and skin discoloration more frequently and females reported urogenital events more often. The overall frequency and severity of other adverse events were comparable.

No dosing modifications based on gender are recommended in the labeling.

Age

Overall age did not affect clinical response. It was not possible to assess safety or efficacy in elderly patients (≥65 years of age) because they accounted for <1% of HIV-1 trial participants. Further, extremely few subjects 65 years of age and older were enrolled in pharmacokinetic studies. Although the numbers of elderly patients with HIV-1 infection is relatively small, there do not appear, from preclinical or clinical studies, any specific contraindications to using Emtriva in this age group. Therefore, no additional dosing modifications based on age are recommended in the labeling.

Renal Impairment

Emtriva® was administered to subjects with normal renal function and to those with End Stage Renal Disease (ESRD) requiring hemodialysis. Results demonstrate that urinary excretion is the primary mode of elimination, and as creatinine clearance decreases Emtriva exposures increase. Emtriva is dialyzable and hemodialysis removes approximately 30% of an emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

The following dosing schedule will be included in the labeling: 200 mg every 24 hours for CrCl ≥50 mL/min, 200 mg every 48 hours for CrCl 30-49 mL/min, 200 mg every 72 hours for CrCl 15-29 mL/min, and for patients with CrCl <15 mL/min and those requiring hemodialysis, 200 mg every 96 hours. On hemodialysis days, Emtriva should be administered following the dialysis procedure.

Use During Pregnancy

Fifty-three pregnancies occurred in women exposed to Emtriva. The majority of pregnancies were electively terminated; however, 19 live healthy births were reported. There were six spontaneous abortions. In all cases, the patient was receiving multiple antiretroviral agents, including Emtriva. Therefore, the specific role of Emtriva in these outcomes could not be determined.

Results of preclinical reproductive and developmental toxicology studies demonstrated no adverse effects on fertility, reproductive performance, sperm count (male rats), mortality or developmental toxicity. The clinical data appear to suggest no specific risk to fetal development.

However, since no adequate well-controlled studies have been conducted in pregnant females, Emtriva® is classified as Pregnancy Category B, with the recommendation that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Emtriva will be included in the ongoing Antiretroviral Pregnancy Registry.

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established name:	Emtricitabine
Trade Name:	Emtriva®
Chemical:	2'3'Dideoxy-5-flouro-3'thiacytadine (FTC)
Class:	Nucleoside analogue
Proposed indication:	Treatment of HIV-1 infection in adults (≥18 years of age)
Dose and regimen:	200 mg once-daily in combination with other antiretroviral agents
Dosage form:	200 mg capsules

B. State of Armamentarium for Indication

There are 18 drugs approved in the US for the treatment of HIV infection.

The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of compounds to exhibit anti-HIV efficacy. Currently there are 6 NRTI's marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), and tenofovir (Viread®, sometimes also referred to as a nucleotide). More recently introduced classes of antiretroviral agents include the non-nucleoside reverse transcriptase inhibitors (NNRTI), including delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®), and the protease inhibitors (PI), now represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®) and lopinavir/ritonavir fixed dose combination (Kaletra®). The most recently approved agents include a GP41 fusion inhibitor (Fuzeon®) and a PI (Reyataz®).

The current standard is to treat with highly active antiretroviral therapy (HAART) that includes at least three drugs, including either a NNRTI or PI with two NRTIs, to attack various stages in the life-cycle of the virus to attempt long-term suppression of viral replication and increases in CD4 cell counts.

Although the introduction of HAART has led to significant improvement in morbidity and mortality, a substantial number of patients do not achieve or maintain adequate suppression of HIV viral replication. Side effects, drug interactions, frequent dosing, pill burden, and complex dietary requirements have been cited as dilemmas facing patients and clinicians.

There has been interest in the possibility that simplification of regimens might improve tolerability and adherence and increase the feasibility of long-term effective control of disease. Although it has not been proven that Emtriva will meet these goals, its availability should offer an additional option for clinicians to consider when attempting to design a more simplified once daily HAART regimen.

C. Important Milestones in Product Development

Emtriva® (emtricitabine, FTC) is a cytosine NRTI with *in vitro* activity specific to HIV-1, HIV-2, and HBV. In cells, emtricitabine is phosphorylated to the 5'-triphosphate (FTC-TP) which is a competitive inhibitor of HIV-1 reverse transcriptase and HBV DNA polymerase. Emtricitabine has the same chemical structure as lamivudine (3TC) except for a fluoride residue at position 5 on the pyrimidine ring. Emtricitabine is reported to have a 10-fold greater *in vitro* potency than lamivudine.[1] Resistance to emtricitabine is the same as described for lamivudine: a single mutation at codon 184 (M184V/I).

Burroughs Wellcome submitted the original IND for Emtriva( )n January 1994. The rights were subsequently licensed to Triangle in 1995, with a new IND submitted in August 1997. In September 1997, the applicant conducted two Phase 1 two-week dose-ranging studies in HIV-infected patients (FTC-101 and FTC-102). The applicant relied on the results of these studies for selection of the proposed dose for use in Phase 3 studies. No Phase 2 studies were conducted.

Fast Track designation was conveyed in August 1998, based primarily on its potential for once daily administration.

On October 8, 1998, a development meeting was held to discuss the design and analysis plans for the applicant's proposed phase 3 studies. The Division could not concur with the proposed overall drug development plan. Specifically, the Division expressed numerous concerns about the utility of the current database from the two Phase 1 studies as the basis for selection of the dose for the Phase 3 studies and the risk to the applicant associated with such a selection. Concerns were raised about the small number of subjects enrolled, the limited duration of dosing, and whether the data on reductions in HIV-1 RNA demonstrated meaningful differences among the doses studied in FTC-101 and FTC-102. It was recommended that the applicant conduct additional dose finding studies or modify the proposed clinical trials to include additional doses of Emtriva. The applicant 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. Further, the Division expressed several reservations about the original designs of FTC-301 and FTC-303.

Study FTC-302 was initiated in September 1999 in the Republic of South Africa (RSA), and was to serve as the applicant's second pivotal study to support the approval of Emtriva. In December 1999, the applicant reported three liver-related deaths and a significant number of serious liver-related adverse events. The Medicines Control Council (MCC) of the RSA terminated the study for significant departures from accepted good clinical practices; the study was placed on CLINICAL HOLD in the US in February 2000. Due to lengthy negotiations between the applicant and the MCC, all patients completed 48 weeks of blinded treatment. Subsequently, the applicant requested that the CLINICAL HOLD be lifted; this request was denied based on the conditions of the CLINICAL HOLD had not

[1] Lamivudine is a NRTI currently marketed by GlaxoSmithKline under the trade names Epivir® and Epivir-HBV® and is one of the active ingredients in the fixed-dose combination products Combivir® and Trizivir®.

been met (see **CLINICAL REVIEW METHODS: D. Were Trials Conducted in Accordance with Accepted Ethical Standards**).

On July 3, 2002, a preNDA meeting was held during which the applicant described the data that would be included in an NDA for Emtriva. The application would include final (48-week) data from study FTC-303 and interim (24-week) data from study FTC-301A. Prior to the meeting, the applicant notified the Division that the interim data from study FTC-301A suggested that one of the blinded treatment arms appeared to convey better antiviral activity and safety compared to the other. Based on a recommendation from the study DSMB, the treatment arms were unblinded; the better performing arm was the arm containing Emtriva. The protocol was amended to offer the Emtriva-containing regimen to all patients. The study was continued until all patients had completed 48 weeks of treatment.

The Emtriva® NDA was submitted on September 3, 2002 and granted a standard review (10 months).

Midway through the review of the NDA Gilead Sciences purchased Triangle Pharmaceuticals, and became the applicant of record for this NDA. In addition, Gilead submitted the new trade name, Emtriva®, as a replacement for Coviracil®.

Indications Not Claimed in the NDA

D. Other Relevant Information

Emtriva is not approved in any other country.

E. Important Issues with Pharmacologically Related Agents

The risk of virologic failure is clearly an important factor in selecting an initial antiretroviral regimen. Other factors such as safety, toxicity, adherence, preservation of future treatment options, access, cost, and other issues also remain important in selecting the optimal first regimen for an individual patient.

A major issue with antiretroviral agents is emergence of resistance. Resistance is widely considered to be partially related to problems in adherence to combination therapy, with irregular gaps in use of individual drugs considered to promote risk of resistance due to periods when the full combination is not present at sufficient levels to block viral replication. A change from

twice daily to once daily dosing has been postulated to be associated with both lower and higher risk of resistance emergence. Specifically, once daily dosing could improve adherence. Conversely, once daily dosing could be detrimental if trough levels were low enough to permit viral replication and were low for prolonged periods with even single missed doses. Most NRTIs do not have the complex dietary requirements or large numbers of doses or pills associated with some other antiretrovirals, so the current application adds little to this issue (would change from one tablet twice daily to one or two tablets once daily, neither with dietary restrictions). Other issues with NRTIs include toxicities such as marrow suppression, neuropathy, pancreatitis, and lactic acidosis with prolonged use. Experience with other drugs does not suggest that number of doses per day is necessarily or uniformly linked to these toxicities, although there may be some associations with both total daily dose and duration of use.

A second major obstacle to long-term therapy is drug toxicity. The nucleoside analogues have both early and late toxicities. Examples of early toxicities include nausea and other gastrointestinal side effects, rash, and CNS side effects. Toxicities that have been related to some NRTIs include anemia, peripheral neuropathy, pancreatitis, lipoatrophy, and lactic acidosis. As a nucleoside analogue, many of these events were expected to occur during Emtriva therapy. The goal, therefore, is to select nucleoside analogues that produce lower frequency and severity of these toxicities. There is a growing body of evidence that the combination of didanosine (ddI) and stavudine (d4T) is falling out of favor as components of initial treatment for HIV infection due to the apparent higher risk of toxicities associated with these two agents. The risk of toxicities, and subsequent discontinuation, when ddI and d4T are used together has been found to be higher than when one of these drugs is used with other nucleoside analogues, such as lamivudine (3TC), thus leading to decreased efficacy. Emtriva, like 3TC, may provide a reasonable alternative for use in combination with ddI or d4T, rather than selecting the combination of ddI+d4T.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Statistics and/or Other Consultant Reviews

2.1. Chemistry

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Lunn's review.

Emtriva® Tablets will be supplied as 200-mg, size 1 hard gelatin capsules with a light blue cap and white opaque body, printed with "200" in black ink on the cap and GILEAD and the cooperate logo in black on the body. The daily recommended dose of Emtriva is one 200-mg tablet one time per day. The composition of Emtriva Tablets is provided in Table 1.

Table 1. Composition of Emtriva® Tablets

Component	Weight (mg)/ Tablet
Emtriva	200.0
Microcrystalline cellulose, NF	—
Crospovidone, NF	—
Povidone, USP	—
Magnesium Stearate, NF	—
Total Weight	400.0

Source: Emtriva® Application Summary, July 31, 2002, amended April 25, 2003.

The process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the pivotal clinical studies. The regulatory specification for Emtriva Tablets includes description, identification, assay, content uniformity, chromatographic impurity/degradation products, polymorphic form, dissolution, and microbial attributes.

The primary stability data generated on three commercial-representative batches indicate that the drug product is generally stable at 25°C/60% relative humidity (RH) for 24 months and at 40°C/75% (RH) for six months. Additionally, 24 months of supportive stability data on three lots of 200 mg tablets prepared using — mg of lactose monohydrate (instead of — mg), — mg of pregelatinized starch (instead of — mg) and no crospovidone (instead of — mg) was submitted. There was no significant time-dependent degradation, and all stability tests were within predetermined specifications. Therefore, the data submitted support a shelf-life of 24 months.

Emtriva Tablets will be packaged in a 60 mL — bottle and a — child-resistant cap lined with an induction — liner. Bottle can be stored at room temperature: 25°C [77°F], with excursions permitted to 15-30°C [59-86°C].

All pre-approval inspections of drug substance and drug product manufacturing and testing sites were determined to be acceptable by the Office of Compliance.

2.2 Pharmacology/Toxicology

For a detailed discussion, please see Dr. Verma's review. In this section, results of studies in which the drug substance, FTC, was used are reviewed.

FTC is phosphorylated to the 5'-monophosphate by cellular deoxycytidine kinase, to the 5'-diphosphate by deoxycytidine monophosphate kinase, and then to the 5'-triphosphate by nucleoside diphosphate kinase. The 5'-triphosphate of FTC competitively inhibits the incorporation of 2'-deoxycytidine 5'-triphosphate into the homopolymeric template primer rI·dC catalyzed by RT. Because the 5'-triphosphate of FTC does not contain a 3'-hydroxyl group, its incorporation into nascent viral DNA results in the chain termination.

3TC undergoes the same phosphorylation process. FTC and 3TC have similar structures with the exception that FTC contains a single fluorine moiety. The fluorine moiety is negatively charged, as are strands of DNA. Thus, FTC may not interact as well with DNA as 3TC.

Animal studies demonstrated:

- The NOEL ranged between 200 mg/kg to 1000 mg/kg depending on species. Based on a body surface area factor, equivalent human doses would be between 4000 mg/day and 10,000 mg/day for a 60 kg person. The daily dose of Emtriva for adults is 200 mg; therefore, the lowest animal dose provides for an approximately 50-fold margin for safety.

- Unchanged FTC represented the great majority of radioactivity present in urine and feces (70-95%), indicating that FTC is not extensively metabolized.

- FTC has a low extent of binding to human plasma at therapeutic concentrations, 4%. Because of the low extent of binding to human plasma at therapeutic concentrations, drug interactions mediated by protein binding displacement are not expected.

- FTC did not affect heart rate or blood pressure, any respiratory functions, urine output, pH or electrolyte excretion, or gastrointestinal motility.

- FTC was not mutagenic, and had a negative micronucleus assay.

- Results of reproductive and developmental toxicology studies demonstrated no adverse effects on male or female fertility, reproductive performance, sperm count (male rats), mortality or developmental toxicity. There are no adequate and well-controlled studies in pregnant women, therefore Emtriva will be classified as Category B.

2.3 Microbiology

For a detailed discussion, please see Dr. Batulla's review.

The presumed mechanism of action of nucleoside analogues is that they are initially metabolized to their respective 5'-triphosphates (dNTPs) by cellular nucleoside and nucleotide kinases. Accordingly, the prodrug, FTC, inside cells is converted into the active drug form, FTC-triphosphaste (TP), by sequential phosphorylations with cellular enzymes. The active form, FTC-TP, competes with natural (physiological) nucleoside triphosphates for the nucleotide-binding site on the viral reverse transcriptase. This competition is believed to inhibit the rate of HIV DNA synthesis (both RNA-directed and DNA-directed DNA polymerase activities of RT) by decreasing the incorporation of the natural deoxyribonucleotides. In addition, FTC-TP also serves as an alternate substrate thereby incorporated into the growing DNA chain of the HIV DNA. Since the incorporated FTC-MP nucleotide lacks the 3'- hydroxyl group, no phosphodiester bond formation can occur with the next incoming nucleotide; consequently, the DNA chain growth stops. Thus, the full-length proviral DNA synthesis that is required for viral DNA integration and establishment of viral infection is prevented.

In vitro and *in vivo* analyses demonstrated:

- FTC is active against various strains of HIV-1, HIV-2, and HBV.
- FTC has a 50% inhibitory concentration (IC_{50}) between 0.001-0.50 μM.
- FTC is more potent than lamivudine, IC_{50}=0.01-0.09 μM versus IC_{50}=0.07-3.2 μM.
- FTC exhibited additive to synergistic activity when combined with delavirdine, efavirenz, nevirapine, abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine, amprenavir, indinavir, nelfinavir, and ritonavir.
- FTC is a weak inhibitor of mammalian DNA polymerase α, β, and ε, and mitochondrial DNA polymerase γ.
- Resistance to FTC develops quickly (within 2-4 passages) and is manifested by a change at codon 184 of the reverse transcriptase with methionine being replaced by valine or isolucene (M184V/I).

III. Human Pharmacokinetics and Pharmacodynamics

For a detailed discussion, please see Dr. DiGiacinto's Clinical Pharmacology review.

A. Pharmacokinetics

For a detailed discussion, please see Dr. Jennifer DiGiacinto's Biopharmaceutics review.
The applicant conducted an extensive development program. Included in the NDA are data from 18 studies that assessed single and multiple-dose pharmacokinetics, effects of dose, repeated administration, formulation, co-administration of food, renal impairment, and interactions with various medications that could be taken by HIV-infected patients.

Relevant findings and issues raised by pharmacokinetic studies that are applicable to the indication include:

- FTC is rapidly and well absorbed following oral administration with a T_{max} of 1.5-2 hours.
- Plasma FTC concentrations achieved levels above the in vitro IC_{90} (0.014 ug/mL) over a 24 hour period.
- FTC is eliminated primarily unchanged in the urine. Sixty to 70% of an oral dose is absorbed and recovered in urine. FTC is actively secreted by renal tubules. Emtriva is dialyzable, as creatinine clearance decreases Emtriva exposures increase. Hemodialysis treatment removes approximately 30% of an emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

- The elimination half-life is approximately 9 hours, which supports QD dosing.
- The rate of absorption is decreased but exposure was not affected following a standard high-fat meal. Therefore, FTC can be administered with or without food.
- FTC is approximately 4% protein bound.
- No clinically significant interactions with famciclovir, stavudine, tenofovir, or indinavir were identified in drug-drug interaction studies.
- A single dose of FTC increased the AUC and C_{max} of zidovudine by 26% and 66%, respectively.

B. Pharmacodynamics

The applicant conducted two studies to assess the multiple dose pharmacokinetics and antiviral activity of FTC. These data supported the antiviral activity at the selected 200 mg QD dose.

In study **FTC-101**, 45 HIV-infected subjects were randomized to receive FTC 25 mg BID, 100 mg QD, 100 mg BID, 200 mg QD or 200 mg BID for 14 days. Pharmacokinetic assessment demonstrated that FTC plasma concentrations increased in a dose proportional manner, FTC triphosphate (FTC-TP) concentrations peaked approximately 6 hours post dose, and FTC-TP concentrations in peripheral blood mononuclear cells also increased in a dose proportional manner. Following 14 days of FTC monotherapy, the median decrease in HIV-1 RNA was -1.4, -1.8, -1.7, -1.9, and -1.8 $\log_{10}$ c/mL for the 25 mg BID, 100 mg QD, 100 mg BID, 200 mg QD and 200 mg BID groups, respectively.

Study **FTC-102** compared the antiviral activity of three doses of FTC to 3TC administered for 10 days. Eighty HIV-infected subjects were randomized to FTC 25 mg QD, 100 mg QD, or 200 mg QD to 3TC 150 mg BID. The mean change from baseline in $\log_{10}$ c/mL HIV-1 RNA were -1.43 for the 25 mg QD dose, -1.52 for the 100 mg QD, and -1.69 for the 200 mg QD doses of FTC compared to -1.5 for 3TC. The applicant concluded that these findings suggested that in large clinical studies FTC-based regimens would provide more robust antiviral responses compared to 3TC-based regimens (see **Description of Clinical Studies**).

IV. Description of Clinical Data and Sources

A. Overall Data

The data to support Emtriva's safety and efficacy for treatment of adults with HIV-1 infection were derived primarily from clinical studies conducted by the applicant. Supportive studies conducted by the French Agence Nationale de Recherches sur le SIDA (ANRS) and the AIDS Clinical Trial Group (ACTG) of US National Institutes of Health were also submitted and reviewed.

B. Tables Listing the Clinical Trials

Table 2 presents a schematic overview of all completed and ongoing clinical studies submitted to support the safety and efficacy of Emtriva.

Table 2. Emtriva HIV Studies

Protocol No. Population Countries	Start Date End Date	Design	Treatment Dose Frequency Duration	No. Patients Treated
FTC-201 (ANRS-091, Montana) Treatment naïve HIV-1 infected adults France	February 1999 Ongoing	Open-label, single-arm	FTC/ddI/EFV 48 weeks	FTC: 40
FTC-301 Treatment naïve HIV-1 infected adults U.S. and Chile	August 1999 November 2000	Randomized, open-label, superiority comparison of FTC to abacavir (ABC)	FTC/d4T/EFV or ABC/d4T/EFV 48 weeks	FTC: 18 ABC: 19
FTC-301A[*] Treatment naïve HIV-1 infected adults U.S., Canada, Mexico, Chile, Brazil, Argentina, UK, France, Germany	August 2000 September 2002	Randomized, double-blind, equivalence comparison of FTC to d4T	FTC/ddI/EFV or d4T/ddI/EFV 48 weeks	FTC: 286 d4T: 285
FTC-302 Treatment naïve HIV-1 infected adults South Africa	August 1999 **Trial terminated early by RSA MCC and placed on CLINICAL HOLD by DAVDP**	Randomized, double-blind comparison of FTC to 3TC	FTC/d4T/NVP or EFV or 3TC/d4T/NVP or EFV 48 weeks	FTC: 234 3TC: 234
FTC-303[*] Treatment naïve HIV-1 infected adults U.S.	September 1998 June 2000	Randomized, open-label equivalence of FTC to 3TC	FTC 200 and current background or Continue 3TC containing regimen	FTC: 294 3TC: 146
FTC-304 (ANRS-099, ALIZE) Treatment experienced HIV-1 infected adults with stable HIV RNA France	June 2000 Ongoing	Open-label switch versus maintenance	Switch: FTC/ddI/EFV Maintenance: continuation of 1 or 2 PIs plus 2 NRTIs 48 weeks	Switch: 177 Maintenance:177

FTC-350 Treatment (3TC) experienced (virologic success) from FTC-303 U.S.	September 1999 Ongoing	Open-label rollover	FTC plus prescribed ART regimen Access until virologic failure or FTC commercially available	FTC: 289
MKC-401 Treatment naïve HIV-1 infected adults U.S., South Africa	August 1999 March 2002	Randomized, open-label comparison of emivirine (MKC) and ABC	Arm 1: FTC/d4T/MKC or Arm 2: FTC/d4T/ABC 48 weeks	Arm 1: 376 Arm 2: 188
ACTG 5015 Treatment naïve HIV-1 infected adults U.S.	October 2000 Ongoing	Open-label age differentiated cohort study	FTC/d4T/Kaletra 48 weeks	FTC: 92

* Denotes pivotal study.

C. Postmarketing Experience

There has been no postmarketing experience with Emtriva® because it is not marketed in any country, nor has a marketing application been submitted to any regulatory agency, other than the FDA.

D. Literature Review

The applicant submitted a comprehensive review of the current state of HIV therapy, articles related to pre-clinical and clinical investigations for Emtriva, and copies of scientific meeting abstracts and posters.

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review of NDA 21-500 (Emtriva® Capsules) was conducted using volumes 1.133-1.150 (ISE and ISS), 1.151 through 1.553 (clinical study reports) and electronic SAS transport files of the NDA submission.

The current indication being considered for this product is treatment of HIV-1 infection in adults >18 years of age. As noted in Table 2 above, the development program to support the safety and efficacy of Emtriva consisted of two pivotal and several supportive studies. Study reports, line listings, and Case Report Forms were reviewed for all efficacy endpoints and demographic subgroups. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of physical examination line listings. 'Clinically significant' laboratory abnormalities were defined as falling outside the 'normal' range values for the parameter by a specified amount defined in the study reports.

An update containing additional safety information (cut off September 1, 2002) and the 48-week results of study FTC-301A were submitted during the review period, as were individual Serious Adverse Event reports from ongoing studies.

Studies to establish pharmacokinetics, safety, and efficacy of Emtriva in HIV exposed patients are ongoing and will be discussed below.

Pertinent positive and negative safety and efficacy findings are discussed in the clinical study reviews. Additional human safety information derived from pharmacokinetics studies and from other specific safety-related investigations is discussed in the integrated summary of safety section. The medical reviewer's recommendations for approval are summarized in the **Conclusions and Recommendations** section.

B. Overview of Materials Consulted in Review

The primary materials consulted included the entire NDA and IND, protocols and reports of studies conducted by the ACTG and the French ANRS that included Emtriva, and responses to requests for additional information to the NDA. The NDA and responses to requests for additional information were submitted in both hard copy and to the electronic document room.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

- **FTC-301A and FTC-303**

The Division of Scientific Investigations (DSI) audited four investigators that participated in the two pivotal FTC studies: Drs. Vilma Vega, David Hass, Robert Wallace, and Larry Bush.

Dr. Hass received a four item 483: one SAE was reported 6 months after the investigator became aware of it, not all adverse events mentioned in the progress notes were transcribed to the adverse event section of the CRF, and two instances of nonadherence to the protocol were detailed.

The DSI audit found no deficiencies at Drs. Vega, Wallace and Bush's sites that could compromise the integrity of the data. DSI concluded that all three investigators adhered to pertinent federal regulations and/or good clinical practices, and all three received NAI letters.

In summary, DSI concluded that no major deficiencies were noted at the sites that could compromise the integrity of the data, and no subsequent actions or follow-up inspections should be undertaken.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Study FTC-302 was terminated early by the Medicines Control Council (MCC) of the Republic of South Africa for patient mismanagement and failure to adhere to good clinical practices. The study was subsequently placed on clinical hold by DAVDP, and the applicant was informed that FTC-302 could not be used as a pivotal efficacy trial. The following is a chronology of important telecoms, meetings, and interactions between DAVDP and Triangle Pharmaceuticals.

In January 2000, DAVDP contacted the Medicines Control Council (MCC) of the Republic of South Africa to inform them of three deaths due to hepatotoxicity and other serious adverse events that had occurred in study FTC-302. On February 2, 2000, representatives of the MCC and FDA discussed the serious nature of the adverse events occurring in FTC-302 in a teleconference. FDA provided the MCC with our response to these events as well as agreements made by Triangle to improve the safe management of patients in the study. The MCC informed us that they would be meeting with the sponsor and the CRO [redacted] responsible for oversight of the conduct of study FTC-302.

On March 8, 2000, the MCC informed DAVDP that the sponsor agreed to amend the protocol to improve safety monitoring, especially for possible hepatotoxicity. Triangle also agreed to provide patients with a telephone card to facilitate contact with study sites; to arrange for home visits if a patient could not come to clinic; and to submit the CV's of all investigators. Finally, [redacted] maximum allowable elevations in hepatic enzymes would be reduced, but no specifics were provided.

Of note, at the meeting between the MCC and Triangle, Triangle was asked about progress in investigating the hepatotoxicity seen in FTC-302, as requested by FDA. The response provided from Triangle to investigators in a letter dated February 22, 2000 stated: "we have assured ourselves that the liver toxicity grade III and IV events were probably related to Nevirapine and remotely related to a drug interaction with the blinded study drugs FTC and lamivudine." No supporting data for this conclusion was provided to the MCC.

At the same time, DAVDP was made aware that Triangle granted 350 protocol exemptions. The main reasons included lower than allowed CD4 cell counts, prolonged time between screening and baseline visits, and various exceptions for out of range laboratory parameters.

On April 6, 2000, the MCC issued a letter to Triangle stating that because of numerous serious protocol violations that compromised the scientific integrity of study FTC-302, the study should be terminated. Triangle was asked to submit a plan to unwind the study within 7 days. Triangle responded that they would enroll no additional patients into the study, but that they preferred to continue the study in a controlled clinical research setting.

The study was placed on CLINICAL HOLD because of questions about the appropriateness of medical management of subjects who experienced adverse events; the inadequacy of investigations and reporting of adverse events; issues with the capacity of the medical infrastructure in South Africa to support the conduct of such a study; the inadequacy of communication between Triangle and the MCC; and the lack of a DSMB or other oversight group to review safety data and make recommendations regarding human subject protection. In order to remove the hold, we requested that Triangle provide documentation of all findings and deliberations of the MCC's review of this trial; documentation of an MCC decision to allow the study to continue; satisfactory inspection of clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings; and establishment of an independent data safety monitoring board (DMSB).

On April 14, 2000, the MCC again informed Triangle that the study was terminated, pointing out that there had been "poor adherence to GCP" and "protocol violations regarding patient recruitment." Further, the MCC requested that patients who had virologic response defined as HIV RNA <2,000 c/mL continue their present regimen on compassionate grounds. Again it was Triangle's position that the safest and most appropriate course of action would be to maintain the blinded therapy.

There were apparently no communications between the MCC and Triangle until June 29, 2000, when Triangle met with the MCC and again requested that the trial continue in a blinded manner.

On August 7, 2000 Triangle was informed by the MCC that the trial had been terminated and the data generated by FTC-302 could not be utilized to support a future registration application, and that the compassionate use recommended by the MCC implied that the study be unblinded.

On September 8, 2000, Triangle submitted a compassionate use protocol. According to Triangle, no response was received from the MCC, and in December 2000, the study was completed in a blinded manner.

On January 15, 2001, Triangle submitted a response to the CLINICAL HOLD letter. The CLINICAL HOLD was maintained because the MCC had not reversed their decision to terminate FTC-302. Therefore, the stipulation to document the MCC's decision to allow FTC-302 to continue was not met. In addition, Triangle had contracted with [redacted] an independent consulting group specializing in Good Clinical Practice audits and evaluations to audit FTC-302. The audit identified a number of deviations from acceptable

standards: the process and documentation of Informed Consent; enrollment of several unsuitable subjects; discrepancies in compliance and drug accountability; unacceptable management and reporting of Serious Adverse Events in several instances; and backlogs of CRF reviews that were "insufficient to maintain currency with study data and developments."

Finally, DAVDP did not agree that the Clinical Steering Committee (CSC) that Triangle had formed was an adequate response to the request that an independent DSMB be established. Specifically, the CSC included both Triangle employees and the principal investigator of the study, which called into question the independence of this committee.

DAVDP also recommended that Triangle withdraw study FTC-302 from their US IND.

DAVDP met with Triangle on April 18 and on June 5, 2001. Triangle maintained they did not interpret "terminated" to mean that the study had to be completely stopped and unblinded until the August 7, 2000 communication from the MCC. Regardless of their interpretation of the communications from the MCC, it was Triangle's position that their study qualifies as an adequate and well-controlled study that would support a marketing application for FTC. DAVDP stated it would be difficult to accept the study as adequate and well controlled to support an NDA since regulatory authorities had terminated the study in the country in which it had been conducted.

Following the April 18, 2001 meeting, DAVDP contacted the Office for Human Research Protection to obtain an opinion on the acceptability of FTC-302 as a pivotal trial in an NDA for FTC. The opinion was that under 21 CFR 312.120(c)(1) and (2), consideration of study FTC-302 as a pivotal trial would not be justified because it did not conform to the foreign country's standards.

On July 13, 2001, Triangle submitted a legal brief prepared by [redacted] describing how the clinical efficacy data from study FTC-302 can be used to support an NDA for FTC. The brief and other documents were reviewed upheld, based on 21 CFR 312.120, that the conditions for lifting the CLINICAL HOLD were not met and that the efficacy data could not be used to support an application for FTC.

Study FTC-302 was reviewed for its contribution to the assessment of Emtriva's safety. No unexpected adverse events related to Emtriva were identified, and the data did not change the overall assessment of Emtriva's safety.

The two pivotal studies, FTC-301A and FTC-303, appear to have been conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. The applicant requested that all investigators and sub-investigators from any studies contained in the NDA that contributed to the assessment of safety and efficacy (covered studies) disclose proprietary interest or significant equity as defined in the regulations. The applicant has

included a list of all investigators and sub-investigators who responded to their request on form 3454.

The applicant disclosed significant financial interests and arrangements for four investigators:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The applicant stated that each of the above individuals were sub-investigators in large double-blind, placebo-controlled multi-center studies, none enrolled sufficient numbers of patients to affect the results of the study, and none was involved in the analysis of the study data. Therefore, the applicant concluded that there was no evidence that these sub-investigators impacted the results of the studies.

Comment: This reviewer concurs that the above financial disclosures did not appear to have impacted outcome of any particular study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

FTC is an active antiretroviral agent, and the results of studies FTC-301A and FTC-303 demonstrate that regimens containing Emtriva administered once daily produced antiviral and immunologic activity in adult patients with HIV-1 infection comparable to other three drug NRTI-based regimens.

However, Emtriva failed to demonstrate a greater antiviral or immunological response when directly compared to 3TC. The results of study FTC-303, in which Emtriva was substituted for 3TC in patients with suppressed HIV RNA, demonstrated no apparent advantage to substituting 3TC for Emtriva. Although it could not be considered a pivotal study, FTC-302 provided a supportive direct comparison of Emtriva to 3TC in treatment naïve patients; the results suggested that Emtriva did not provide a more robust antiviral response as suggested by the applicant based on the results of a dose-ranging study (Study FTC-102).

The results of study FTC-303 suggest no therapeutic advantage for Emtriva® over 3TC in patients who are virologically suppressed a 3TC-containing regimen. In study FTC-303, discontinuations due to adverse events were more common amongst patients who switched to Emtriva. A possibility for the poorer results in two comparative studies is the presence of a fluorine moiety on the FTC molecule. This fluorine moiety is negatively charged, as are viral DNA strands, Emtriva may not have interacted as well with viral DNA further leading to less chain termination potency.

Study 301A demonstrated that the regimen of Emtriva+ddI+EFV was active and better tolerated than the comparator regimen of d4T+ddI+EFV. This was quite consistent with other studies that showed that regimens containing lamviudine and efavirenz are extremely effective and that ddI+d4T is a more toxic backbone and when combined with efavirenz, is associated with worse virologic outcomes.

B. General Approach to Review of the Efficacy of the Drug

The principal focus of review was the two pivotal studies, FTC-301A and FTC-303. Supportive controlled and uncontrolled studies were evaluated for any usable efficacy information.

C. Detailed Review of Trials by Indication

Treatment of HIV-infected adults is the only indication being sought in the current application. The two pivotal efficacy studies (FTC-301A and FTC-303) submitted in support of this indication are reviewed in detail. Brief reviews of additional controlled and uncontrolled supportive efficacy studies are also presented below.

C.1 Review of Pivotal Efficacy Studies

C.1.a Study FTC-303

"A Randomized, Open-Label Equivalence Study of FTC Versus Lamivudine in Patients on a Stable Triple Antiretroviral Therapy Regimen Containing Lamivudine, Stavudine or Zidovudine, and a Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor."

FTC-303 was conducted between September 1998 and May 2000, in 43 sites in the US.

- **Objectives**

The primary objectives were to compare: (1) plasma HIV RNA AAUCMB between treatment arms after 24 weeks of treatment; (2) the proportion of subjects in each treatment arm who maintained virologic success at week 48 (defined as continued suppression of HIV RNA to <400 copies/mL); and, (3) the proportion of subjects who discontinued therapy over 48 weeks.

Secondary objectives included comparisons of: (1) time to virologic failure; (2) time to effectiveness failure; (3) the proportion of effectiveness failures; (4) the proportion whose HIV RNA remained <50 copies/mL; (5) the proportion who remained on the randomized treatment arm; (6) AAUCMB between FTC and 3TC; (7) CD4 and CD8 cell counts; (8) the percentage

increase above baseline; (9) population pharmacokinetics; and, (10) reverse transcriptase genotype of isolates from virologic failures.

- **Design**

FTC-303 was a phase 3 open-label, multi-center, randomized, equivalence study. Patients were to be on a stable triple antiretroviral background therapy consisting of lamivudine (3TC) with zidovudine (ZDV) or stavudine (d4T) and a protease inhibitor (PI) for ≥12 weeks or a non-nucleoside reverse transcriptase inhibitor (NNRTI) for ≥8 weeks, with HIV RNA <400 c/mL. Following screening, patients were randomized 2:1 to replace 3TC with Emtriva or remain on 3TC as described below:

Arm 1: switch 3TC to Emtriva 200 mg qd with current background regimen.
Arm 2: continue on current 3TC 150 mg bid containing regimen.

Randomization was stratified based on HIV RNA levels and concomitant antiretroviral therapy: <50 copies/mL + PI, <50 copies/mL + NNRTI, 50-400 copies/mL + PI, and 50-400 copies/mL + NNRTI. The duration of dosing was 48 weeks with comparisons of virologic outcomes at weeks 24 and 48.

- **Demographics and Disposition**

The applicant enrolled 459 HIV-1 infected male and female patients 18 years of age and older with plasma HIV RNA of <400 copies/mL on stable antiretroviral therapy containing 3TC plus d4T or ZDV, and a PI or NNRTI were enrolled: 307 to Emtriva and 152 to continued 3TC. Of the 459, 440 (294 Emtriva and 146 3TC) received at least one dose of study medication.

At study entry, 86% were male, 64% were Caucasian, 21% were black, and 13% were hispanic. The mean age of study patients was 42 years (range 22-80). Patients entered with a median duration of prior antiretroviral therapy of 37.3 months in the Emtriva arm and 31.3 months in the 3TC arm. The mean baseline CD4 cell count was 527 cells/mm^3 (range 37-1909 cells/mm^3). At randomization, 86% had HIV RNA <50 c/mL and 14% were between 50 and 400 c/mL.

Twenty-nine and 23% had a history of a CDC class C AIDS-defining event at baseline in the Emtriva and 3TC arms, respectively.

Approximately 70% of patients in both treatment arms had been on antitretroviral regimens prior to their current stable 3TC-containing regimen. More patients in the Emtriva arm had received prior ddI (25%) and nelfinavir (8%) compared to those in the 3TC arm, 15% and 3%, respectively. The arms were well balanced with respect to other PIs and NNRTIs.

Comment: The two arms were similar in baseline demographic and disease characteristics, and represented a population of relatively healthy HIV-infected individuals. It does not appear that the applicant could support an argument that the longer duration of previous antiretroviral therapy contributed to higher rates of virologic failure in the Emtriva arm because the overall virologic failure rates were comparable (see below). Further, although

for a high proportion of patients the entry regimen was not their first regimen, there was no data submitted as to the reasons for changes in the previous regimen(s), i.e., changes due to virologic failure or adverse events. Thus, it is difficult to reach a firm conclusion that these patients represent a more advanced population of HIV infected patients.

Overall compliance with study medication, as assessed by investigators was high, median 98% in both treatment arms. When assessed by drug accountability records, compliance was again similar between treatment arms, median 90%.

Patient disposition is described in Table 3.

Table 3. Patient disposition through 48 weeks

	Emtriva®	3TC
Randomized	307	152
Received at least one dose	294	146
Completed 48 weeks	227 (77%)	119 (82%)
Discontinued	67	26
Adverse event	14 (5%)	0
Non-compliance	4 (1%)	0
Virologic failure	20 (7%)	11 (8%)
Protocol violation	5 (2%)	4 (3%)
Withdrawal request	15 (5%)	9 (6%)
Death	0	1 (1%)
Other	8 (3%)	2 (1%)

Comment: The reasons for premature discontinuation were comparable between treatment arms. More patients discontinued Emtriva due to adverse events. A few discontinuations warrant mention. In two cases, patients discontinued Emtriva due to gastrointestinal events that resolved following replacement of Emtriva with 3TC. In one case, a patient discontinued Emtriva due to anemia, despite having received ZDV (known to cause anemia) for over 2 years.

There may have been bias against Emtriva due to the open-label design; e.g., patients were more likely to discontinue Emtriva because of the impression that new adverse events may be related to the introduction of this new drug. Further, patients who would not tolerate 3TC would have discontinued use of 3TC prior to entry into this study, again introducing bias against the new regimen.

- **Outcome Assessments and Results**

For a detailed review of all efficacy parameters, please see Dr. Zhou's statistical review.

The intent-to-treat population was to have HIV RNA <400 c/mL at baseline. The primary endpoint was a comparison of the stratum adjusted proportion of subjects with continued suppression of HIV RNA <400 c/mL at week 48. The study was powered to provide 80% power to reject the null hypothesis that the difference in 48 week virologic response would be >12.5% in favor of 3TC.