SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Emtriva. For information on changes after approval please refer to module 8.

1. Introduction

Over the last few years, a decrease in the morbidity associated with AIDS and an increase in survival times in association with sustained suppression of viral replication has been achieved in North America and Europe, primarily because of the use of highly active antiretroviral therapy (HAART). Most commonly HAART consists of two nucleoside/nucleotide analogue inhibitors of HIV-1 reverse transcriptase (NRTIs), plus either one or two protease inhibitors (PIs) or a non-nucleoside inhibitor of reverse transcriptase (NNRTIs). The choice of the compounds depends on the status of the patient in terms of plasma viral load (HIV RNA), CD4 cell counts, previous treatment(s), prior relapse and intolerance to treatment.

The long-term use of all these products is, however, limited by the emergence of resistance, by toxicity and by inconvenient dosing schedules or formulations. Further therapeutic agents are therefore clearly needed, particularly in patients who have failed therapy.
Although there is currently not enough data to demonstrate the relative benefit of the many different dosage regimens it is reasonable to accept that a reduced number of daily doses along with a small number of pills may meet the patient's preference.

Emtriva is a new NRTI, which contains emtricitabine as the active substance, which is available in two formulations (200 mg hard capsules and 10 mg/ml oral solution) both intended to be used as a one daily dosage regimen.

The approved indication is " for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents. This indication is based on studies in treatment-naïve patients and treatment-experienced patients with stable virological control. There is no experience of the use of Emtriva in patients who are failing their current regimen or who have failed multiple regimens.
When deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate."

2. Chemical, pharmaceutical and biological aspects

Composition

Hard capsule

Emtriva is presented as hard capsules containing 200 mg of emtricitabine.
The other ingredients include cellulose microcrystalline, crospovidone, povidone, magnesium stearate, hard gelatin capsule shell, indigotine (E132), titanium dioxide (E171) and printing ink.
The capsules are packed either in a high density polyethylene (HDPE) bottle with an induction seal and a child resistant polypropylene cap or in polychlorotrifluoroethylene (PCTFE)/ polyethylene(PE)/ polyvinylchloride(PVC)/ aluminium blisters.

Oral solution

Emtriva is also formulated as an oral solution containing 10mg/ml of emtricitabine.
The other ingredients include cotton candy flavouring, disodium edetate, hydrochloric acid, methyl parahydroxybenzoate, propylene glycol, propyl parahydroxybenzoate, sodium hydroxide, sodium phosphate monobasic monohydrate, sunset yellow (E110), purified water and xylitol.

The oral solution is presented in a multiple use polyethylene terephthalate (PET) bottle with a polypropylene child resistant cap. A measuring cup is supplied.

Active substance

Emtricitabine is a novel nucleoside reverse transcriptase inhibitor. It is a synthetic nucleoside analogue of cytosine.

It is a white to off-white crystalline powder freely soluble in water. The active substance contains two chiral centres, and is produced as a single enantiomer.
In laboratory studies three polymorphic forms I, II and III have been observed. However, only the crystalline form I, which is the most thermodynamically stable, has been produced by the intended commercial process and used in non-clinical and clinical studies.

Two different manufacturers through a three-step synthesis using a stereoselective reaction and enzymatic chiral resolution prepare Emtricitabine.
Satisfactory viral safety data have been provided to support the use of the pig liver esterase. Testing for potential adventitious viruses as well as originating species are part of the specification of this reagent. Moreover, the viral validation study performed using relevant model viruses demonstrates its capacity to inactivate and/or remove potentially contaminating viruses.
The final purification step is carried out by crystallisation from isopropyl acetate. Following crystallisation, the product is washed, dried and milled.
Satisfactory specification and associated methods have been provided for the starting materials, key intermediates, reagents and solvents.

Active substance specification

The active substance specification includes tests for appearance, clarity and colour in solution (Ph Eur), identity (IR and chiral HPLC), assay (HPLC, 98,0% - 102.0%), stereochemical purity (chiral HPLC), related substances (HPLC), residual solvents (GC), water content (Ph Eur), heavy metals (Ph Eur), sulphated ash (Ph Eur) and particle size.
Specification limits have been adequately justified by analytical, stability and toxicity data. Particle size is part of the specification, but is not expected to be a critical parameter with regards to the bioavailability of the capsule, taking into account the high water solubility and high permeability of the active substance. The analytical methods used in routine controls have been suitably described and validated.

Batch analysis data for batches manufactured by the commercial route have been provided for the two synthesis sites (n=12 and n=5) and confirm satisfactory compliance and uniformity with the proposed specification.

Stability

Four batches synthesised at one synthesis site only have been studied under long-term conditions (25°C/60%RH - samples packed in two black antistatic bags placed into tightly closed HDPE container). 24-month data are available for one batch and 18-month data are available for the three other batches. Accelerated stability studies (40°C/75%RH) were performed over a 6-month period.
A photostability study was also performed and showed that the active substance is not light sensitive.
The results obtained support the proposed retest period when stored in two black antistatic bags placed into tightly closed HDPE container.

Other ingredients

Hard capsule
All the excipients comply with the Ph Eur requirements. The in-house specifications presented for the capsule shell, indigotine and the printing ink are satisfactory.
Regarding the TSE risk, satisfactory certificates of suitability have been provided for the magnesium stearate and the gelatin capsule shell. The potential conventional virus risk associated with the pig liver esterase used in the synthesis of the active substance has been satisfactorily addressed (see active

substance). Satisfactory specifications have been provided for the HDPE bottle and the PCTFE/PE/PVC/aluminium blister.

Oral solution
All the excipients comply with the Ph Eur requirements. The in-house specifications presented for the cotton candy flavouring, sodium phosphate monobasic monohydrate and sunset yellow (E110) are satisfactory.
Regarding the TSE risk, the oral solution does not include any components of ruminant origin. The potential conventional virus risk associated with the pig liver esterase used in the synthesis of the active substance has been satisfactorily addressed (see active substance).
The polyethylene terephthalate (PET) bottle and the polypropylene child resistant cap are adequately controlled.

Product development and finished product

Hard capsule
This oral dosage form is of standard formulation and has been developed to release the active substance rapidly prior to absorption.
The initial capsule formulations (prototype 25 mg, prototype 100 mg and formulation "C" 100 mg) were prepared by simple direct blend process. Later on, a wet granulation process (formulation "B" or commercial formulation) was developed and chosen over direct blend in order to achieve the required density and flow properties for the powder blend to allow manufacture on an automated capsule filler. Water content of the granules, density and particle size distribution have shown to have no significant effect on capsule in-vitro dissolution and content uniformity.
All the excipients selected are commonly used. The function of each excipient and the rationale for its use has been satisfactorily described.

Bioequivalence has been demonstrated between the formulation used in clinical trials and the formulation intended for market.

The manufacturing process involves standard pharmaceutical unit operations: preblending, high shear wet granulation, drying, milling, final blending, encapsulation and packaging.
Validation data have been provided for six batches including one production-scale batch. Satisfactory in-process controls have been established.

The product specification include tests for appearance, identity (HPLC, TLC), assay (95.0-105.0% release and 92.0-105.0% shelf life), water content, impurity content, content uniformity (Ph Eur), dissolution, and microbial quality (Ph Eur).

Batch analysis data presented for 16 batches used in clinical studies comply with the specification and confirm the robustness and reproducibility of the manufacturing process.

Long term and accelerated stability studies have been conducted on three primary stability batches. 24-month data are available for one batch and 18-month data for the two others under long-term conditions (25°C/60%RH - bottle and blister intended for commercialisation). Studies under accelerated conditions (40ºC/75%RH – packaging intended for commercialisation) have been performed over a 6-month duration. 18-month data are available for 2 batches packed in blister and 1 batch packed in bottle under intermediate conditions (30ºC/60%RH).
A photostability study has also been performed and shows that the product is not light sensitive.
The results presented support the proposed shelf life and storage conditions defined in the Summary of Product Characteristics.

Oral solution
This formulation was mainly designed for children and adolescents who have difficulties in swallowing. Its development was facilitated by the high intrinsic aqueous solubility of the active substance.

The main issue to be dealt with during development was the pH-induced degradation of emtricitabine, most stable at pH 7.2, and that of the preservative system selected (methyl parahydroxybenzoate and propyl parahydroxybenzoate), more stable at lower pH. A satisfactory balance between the stability of these three components was achieved at pH 7.2 under refrigeration. A phosphate buffer system was incorporated to maintain the pH over the shelf life of the product. Antimicrobial efficacy of the preservative system has been demonstrated according to Ph Eur.
As many oral liquid formulations for paediatric population, it was preferred to be sugar-free, alcohol-free, with a flavour and sweetness consistent with general preferences of children. Xylitol was selected over sorbitol as sweetening agent, because of its lower laxative effect. The colour of the solution being variable, the inclusion of sunset yellow is justified on grounds of product consistency.

A bioavailability study was performed to compare the hard capsule and the oral solution. Under fasting conditions, the absolute bioavailability of the proposed commercial capsule formulation containing 200 mg of emtricitabine was estimated to be 93%, whereas that of the oral solution containing 10 mg/ml of emtricitabine was 75%, giving a relative bioavailability of the capsule *vs* oral solution of 124%. This result is not in line with the known effect of solid *vs* liquid formulation; the reason for it remains unknown.

The method of manufacture can be divided into 8 operations: dissolution of the cotton candy flavouring and parabens in propylene glycol, addition of this solution to purified water containing xylitol, sequential addition of the other excipients, pH adjustment, filtration, de-aeration, filling and packaging. Based on validation data demonstrating chemical stability of the bulk solution, a satisfactory holding time and conditions has been defined.
Validation data have been provided for three production-scale batches.

The product specification include tests for appearance, identity (HPLC, TLC), assay (95.0-105.0% release and 92.0-105.0% shelf life), assay of methyl parahydroxybenzoate, assay of propyl parahydroxybenzoate, assay of EDTA, impurity content, pH, deliverable volume and microbial quality.

Batch analysis data presented for 5 batches used in clinical studies comply with the specification and confirm the robustness and the reproducibility of the manufacturing process.

Long term and accelerated stability studies were conducted on three commercial batches. 18-month data are available for two batches and 12-month data for the third batch under long-term conditions (5ºC – packaging intended for commercialisation). Studies under accelerated conditions (25ºC/40%RH – packaging intended for commercialisation) have been performed over a 6-month duration. A photostability study has also been performed. Thermal cycling study (cycling between -15ºC and 40ºC/15%RH for 12 days) and a "material move study" (3 months at 5ºC move to 25ºC/40ºC for 2-4 months) have also been performed.
Antimicrobial efficacy of the preservative system has been demonstrated at the end of shelf life.
The results presented support the proposed shelf life and storage conditions defined in the Summary of Product Characteristics.

3. Toxico-pharmacological aspects

Pharmacodynamics

- Mechanism of action

Emtricitabine is the (-) enantiomer of a dideoxy analogue of cytidine, a pyrimidine nucleoside, structurally related to lamivudine. It is a potent and selective inhibitor of HIV-1 RNA-dependent DNA polymerase (reverse transcriptase). Emtricitabine is sequentially phosphorylated intracellularly to the 5'-monophosphate by cellular deoxycytidine kinases, to the 5'-diphosphate by deoxycytidine monophosphate kinase, and then to the 5'-triphosphate, most likely by the 3'-phosphoglyceride kinase. The antiviral properties of emtricitabine 5'-triphosphate result from competitive inhibition of the incorporation of 2'-deoxycytidine 5'-triphosphate by the HIV reverse transcriptase. Because the 5'-

triphosphate of emtricitabine does not contain a 3'-hydroxyl group, its incorporation into nascent viral DNA by HIV reverse transcriptase results in chain termination, and consequently to inhibition of viral replication.

Emtricitabine 5'-triphosphate has a high selectivity for inhibition of RNA-dependent DNA activities of HIV-RT. It is a weak inhibitor of human DNA polymerase α, β, γ and ε. The Ki value (0.17 ± 0.03 μM) for HIV-1 reverse transcriptase is 35-, 100-, 35-, and 882-fold less than the Ki values measured for cellular DNA polymerases α, β, γ and ε respectively.

- *In-vitro* studies

Emtricitabine has been shown to be specific for HIV-1, HIV-2 and HBV.
Studies in established human T-cell lines and peripheral blood mononuclear cells have demonstrated that emtricitabine was active against laboratory and clinical isolates of HIV-1, including virus with reduced sensitivity to other nucleoside reverse transcriptase inhibitors. The concentration of emtricitabine required to inhibit 50% of the viral replication (EC_{50} values) of laboratory adapted strains of HIV-1 and HIV-2 ranged from 0.0013 to 0.5 μM and 0.08 to 1.5 μM, respectively, depending on cell type and virus strain used in the assay. With clinical isolates of HIV-1, EC_{50} values ranged from 0.002 to 0.028 μM. EC_{50} values were comparable for all subtypes of HIV-1 tested. Addition of human serum or human serum plus alpha-1-acid glycoprotein (AAG) (1 mg/ml) did not alter the EC_{50} value. Increasing the multiplicity of infection caused a modest change in the EC_{50} values.

Compared to other nucleoside analogues, emtricitabine showed greater in-vitro anti-HIV activity than lamivudine, with a difference of sensitivity ranging from 3 to 11 fold, as well as zalcitabine, stavudine, abacavir and didanosine.

- *In-vivo* studies

The *in-vivo* antiviral activity of emtricitabine has been described in the published literature. Severe combined immunodeficient (SCID) mice were reconstituted with human PBMCs and subsequently infected with HIV-1_{A018}. Emtricitabine (30 mg/kg b.i.d. given i.p.) completely inhibited viral infection. In a separate study, using the same mouse model infected with HIV-1_{A018}, both emtricitabine and lamivudine at oral dose levels of about 60 mg/kg/day for 7 days reduced viral loads to a similar extent.

- Viral resistance

The emergence of viruses resistant to emtricitabine has been examined *in vitro* by serial passage of the virus in humans PBMCs in the presence of increasing emtricitabine concentrations. Resistance to emtricitabine developed more slowly than resistance to lamivudine under similar conditions. After week 5 of passaging, emtricitabine retained up to 10-fold potency over lamivudine. Resistance developed as the result of base changes at codon 184 causing the methionine to be changed to a valine (M184V). An isoleucine intermediate has also been observed. The mutant virus was highly resistant to emtricitabine and lamivudine (x 100 fold increase in EC_{50} values) and slightly less sensitive to inhibition by didanosine and zalcitabine (3-fold increase in EC_{50} values). Conversely, viruses resistant to zidovudine, zalcitabine, didanosine, and NNRTI retained their sensitivity to emtricitabine (EC_{50} values = 0.002 μM to 0.08 μM).

- Pharmacodynamic interactions

Potential interaction between emtricitabine and other NRTIs that are converted to active substance via intracellular phosphorylation has not been directly evaluated, however emtricitabine showed *in vitro* additive to synergistic effects in combination with all NRTIs tested. The same was observed with PIs and NNRTIs tested.

- General and safety pharmacology programme

A comprehensive range of safety pharmacology studies revealed no treatment-related adverse effects on any organ system at systemic exposure levels much higher than those anticipated in patients at the recommended clinical dose (10 to more than 50 fold). No effects on the cardiovascular system have been reported in anaesthetised dogs given a cumulative dose of 38.5 mg/kg emtricitabine intravenously over 1 hour period. In addition, there were no abnormalities reported on the ECGs data obtained from the repeated dose toxicity studies in monkeys, where AUC exposures were up to 26 fold higher than in humans given 200 mg dose.

Pharmacokinetics

The pharmacokinetics profile of emtricitabine was evaluated in the mouse, rat and cynomolgus monkey, along with additional published literature. Doses were administered both by oral gavage and i.v. in each study to enable comparison of absolute and relative bioavailability. Only single dose pharmacokinetics studies have been conducted. Toxicokinetic data were derived from selected repeated dose toxicity studies. Emtricitabine levels in plasma were measured by LC/MS. All the pharmacokinetic studies, except for data from the published literature, were conducted in accordance to Good Laboratory Practices.

Absorption and distribution

Emtricitabine was rapidly and extensively absorbed in mice, rats and cynomolgus monkeys after single oral doses ranging from 10 to 600 mg/kg. Oral bioavailability in the three species ranged from 58 % to 97 % and peak plasma levels was reached between 0.5 and 2.5 hours after dosing. C_{max} values ranged from 2.4 to 139 µg/ml and were generally 6 to 10-fold lower than the peak concentrations after comparable i.v. doses. C_{max} and AUC values increased nearly proportionally with the dose over the range 10 to 600 mg/kg. There was a trend towards slower and less extensive absorption at the highest dose levels, however these represent multiples of the proposed human dose (approximately 2-4 mg/kg). Some variability was observed in the rate and extent of oral bioavailability between species, dose levels and fed versus fasted animals. Since emtricitabine was not extensively metabolised in these species, its incomplete bioavailability is most likely due to incomplete absorption rather than to significant first-pass metabolism.

The pharmacokinetic profile of emtricitabine after repeated doses administration was similar to that after single dose administration and there was no sign of accumulation.

Emtricitabine was widely distributed in the body of the three species. After oral administration, the greatest concentrations were found in the gastrointestinal tract and kidneys, which is consistent with its absorption and elimination via these tissues, but also in the liver. The volumes of distribution were high and similar across species (Vdss 0.8 – 1.5 l/kg after i.v. administration) showing the marginal dose-dependency over a wide range of doses (10-600 mg/kg). Vdss was slightly larger than total body water in all species, suggesting that emtricitabine was distributed to both intra-and extra-cellular fluid spaces. Binding of emtricitabine to plasma proteins was low (4%) in all the species studied over a wide range of concentrations. Emtricitabine did not bind to melanin. Emtricitabine showed limited penetration to central nervous system with levels reaching 5 to 10% those in the plasma. Studies in pregnant mice and rabbits demonstrated that emtricitabine crossed the placenta barrier. Foetal/maternal exposure ratios were about 0.4 in both species.

Chiral conversion of emtricitabine in plasma has not been evaluated however it has been shown that this is unlikely to occur in humans, and in the event it occurred it would be of no clinical significance.

Metabolism and elimination

Emtricitabine was nearly completely eliminated 72 hours after dosing with no sign of tissue accumulation.

After oral administration in mice and rats, an average of 67-79 % of the dose was excreted in the urine mainly as unchanged parent compound (about 90 %). In monkeys an average of 40 % of the dose was excreted in the urine, with 64 % as unchanged parent compound. In the 3 species metabolism accounted for only a minor proportion (<10%) of emtricitabine elimination.
The metabolites appeared to be almost exclusively cleared by renal excretion since only trace (<1% of the applied dose) were found in faeces. Metabolism was similar across species and the principal metabolite identified was a 3'-sulfoxide diastereomers, accounting for approximately 2% of the dose in mice, 2.6% in rats and 6-11% in monkeys. Seven other metabolites were detected in the urine of rats and two others in cynomolgus monkeys, none accounting for more than 2% of the dose. These minor metabolites may include a diastereomeric 3'-sulfoxide, a glucuronide conjugate, and deaminated metabolites. The enzymatic system responsible for the formation of 3'-sulfoxides has not been identified, however considering that metabolism is only a minor elimination pathway for emtricitabine, any metabolic interactions with co-administered substances are considered unlikely.
The total body clearance of emtricitabine exceeds the glomerular filtration rate, indicating that it is actively secreted by renal tubules into the urine.

Toxicology

The toxicological programme included single-dose studies (mice and rats), repeated-dose toxicity studies (mice, rats and cynomolgus monkeys), reproductive and developmental toxicity studies (mice, rats and rabbits), genotoxicity, cytotoxicity and immunotoxicity. Carcinogenicity studies in mice and rats are ongoing.

All toxicology studies were performed with emtricitabine free base, which was administered in either distilled water or 0.9% saline or 0.5% methylcellulose. All toxicity studies used the intended clinical route (oral) of administration except two i.v. single dose studies.
The main toxicity studies were conducted in accordance to Good Laboratory Practices.

Single dose toxicity

Single dose toxicity studies were conducted in mice and rats, using oral dose levels ranging from 1050 to 4000 mg/kg and i.v. dose levels ranging from 200 to 700 mg/kg. These were the highest feasible dose levels based on solubility of emtricitabine in vehicle and maximum tolerated volume which could be administered. There were neither deaths nor any overt signs of toxicity observed at any of the doses tested.

Repeated dose toxicity

Repeated-dose toxicity studies were conducted in mice (2 weeks, 1 and 6 months), rats (3 months) and cynomolgus monkeys (1, 3 months and 1 year) using oral doses ranging from 120 to 3000 mg/kg/day. Overall, emtricitabine was well tolerated at systemic exposure levels higher than those expected in humans at the clinical dose. Treatment related effects were limited to high dose groups only and primarily consisted of changes in the red blood cell parameters. These changes which were reported in mice, rats and monkeys (only in 1 year study) were interpreted as mild regenerative anaemia.

Other effects were changes in various organ weights in rodents (pituitary, ovary, thyroid, parathyroid, testes, thymus, spleen and kidney) without any obvious pattern across species or dose level and with no concomitant histopathological changes (1 and 6 months in mice and 3 months in rats). There was increased urine volume in mice (6 months) without any concomitant histopathological renal changes and soft faeces in the monkey (1 month and 3 months). In several cases the effects observed were reversible after a treatment free recovery period. The lowest NOELs for the longest treatment period in each species were 500 mg/kg/day in mice (6 months), 600 mg/kg/day in rats (3 months) and 200 mg/kg/day in monkey (1 year). These doses gave AUCs corresponding to 34-, 33- and 10- fold human AUC (9.60 hr•μg/ml) respectively at the recommended clinical dose of 200 mg once-daily.

Genotoxicity

Emtricitabine was neither genotoxic in two separate bacterial reverse mutation assays (*S. typhimurium* and *E. coli* strains with and without metabolic activation with rat liver S9 fraction) nor in an in-vitro mouse lymphoma assay with concentration up to 5000 µg/ml, in contrast to other NRTIs. Emtricitabine was not clastogenic in an oral mouse micronucleus assay conducted at dose levels up to 2000 mg/kg.

Carcinogenicity

Carcinogenicity studies in the mouse and rat are ongoing using a high dose level providing AUC exposures 25 times human exposures at the clinical dose. The CPMP considered the justification from the applicant to submit the application without final results of carcinogenicity studies. In view of the good safety profile as demonstrated in preclinical tests, the lack of signals for concern (for instance lack of neoplastic or pre-neoplastic lesions in chronic toxicity studies, lack of genotoxicity both *in vitro* and *in vivo*, lack of immunotoxicity), and the therapeutic indication, the CPMP considered that the lack of final results should not preclude the granting for a marketing authorization. The applicant however undertook to provide these final as part of the follow-up measures to be fulfilled post-authorisation.

Reproductive toxicity

Fertility studies in mice and rats did not reveal any treatment-related adverse effects on reproductive function. The NOELs were > 1000 mg/kg/day in mice and 750 mg in rats respectively.

There was no evidence of embryo-foetal toxicity in the mouse study and the NOEL for systemic and developmental toxicity was 1000 mg/kg/dose. In rabbits, reversible treatment-related effects on maternal body weight were observed at 300 mg/kg/day and decreased defecation was observed at 1000 mg/kg/day. The NOEL in pregnant rabbits for maternotoxicity was 100 mg/kg/day.

A pPre and post-natal toxicity study in mice revealed no treatment related effects. The only effect in F1 dams originating from 1000 mg/kg/day F0 dams was a slightly longer oestrus cycle (average 4.9 days as compared to 4.3 days for control). Although statistically significant ($p< 0.001$) this was considered of limited clinical relevance. A NOEL of 500 mg/kg was established in this study.

Other toxicities

An immunotoxicity study was conducted and there was no effect on the immune system as evaluated by IgM antibody response in the rat to sheep red blood cells with doses up to 1000 mg/kg/day corresponding to human exposure of approximately 48-fold at the recommended dose.

Emtricitabine was not cytotoxic to various human lymphocytic and monocytic cell lines or hepatocytes at concentrations much greater than the human C_{max} at the recommended dose (more than 20 fold). Emtricitabine was much less toxic to human bone marrow progenitor cells than two comparators (zidovudine and 2'CDG) and was of comparable toxicity to lamivudine. The CC_{50} (50% cytotoxic concentration) of emtricitabine for human erythroid and granulocyte/macrophage precursor cells was much lower than the anticipated peak human exposure (C_{max}) of around 2 µg/ml at the 200 mg daily dose, thus the data may suggest a low potential for emtricitabine to produce effects on bone marrow at the low exposures required to treat HIV infection.

Considering the variable ability of NRTIs to inhibit the DNA polymerase gamma (Pol γ), which is responsible for replication of mitochondrial DNA (mt DNA), resulting in mtDNA depletion and leading to organelle dysfunction, the mitochondrial toxicity of emtricitabine was evaluated.
Emtricitabine did not reduce the ratio of mitochondrial to cellular DNA in Molt-4 cells nor cause cell death at concentrations up to 100 µM after 7 days continuous exposure. Emtricitabine did not affect mitochondrial DNA content in human Hep G2 and MT2 cells. Emtricitabine also produced no signs of mitochondrial toxicity in liver, heart or skeletal muscle in chronic toxicity studies in mice and cynomolgus monkeys. Neurophysiological measurements performed in monkeys were normal after 1,

3 and 12 months. There were no neurohistological lesions in a variety of CNS and PNS tissues at 3 months treatment at 1000 mg/kg/day.

Impurities
Related substances in emtricitabine substance have been toxicologically qualified. A concern was raised however with respect to the lack of justification for the proposed limit for the primary degradation product (FTU) in the finished product (0.8 % in the hard capsule and 1.0 % in the oral solution). Based on additional toxicology data, including the negative results from additional genotoxicity studies using emtricitabine sample containing FTU 1 % (w/w) (gene mutation and chromosomal aberration), and analytical data, the proposed limits were considered toxicologically justified.

Environmental risk assessment

An assessment of the risk was performed and no significant risk to the environment related to the use of emtricitabine is anticipated.

4. Clinical aspects

The clinical development programme consisted of:

- studies aiming to characterise the pharmacokinetics of emtricitabine in various populations (healthy adults, HIV infected adults and children and patients with renal impairment)
- two short term studies that evaluated emtricitabine monotherapy in HIV-infected subjects and explored various dose regimens
- three phase III sponsored studies in treatment-naïve patients and treatment-experienced adult patients with stable virological control. There were also supportive data from several other studies in adults.
- two ongoing studies in treatment-naïve and experienced children aged from 4 months to < 18 years. Data were provided for up to 24 weeks therapy during the assessment of the application. Children received either the oral solution or the capsules according to weight.

Data regarding the use of emtricitabine in treatment-experienced patients are restricted to switching patients who were responding to their existing regimen to an emtricitabine-containing regimen. There are currently no data on the use of emtricitabine in patients who are failing their current therapy and patients who have failed multiple regimens.

Data from completed studies in patients infected with HBV have been submitted to provide relevant information to the use of emtricitabine in patients who are co-infected with HIV and HBV.

Over 2,000 HIV-infected patients have received emtricitabine in various clinical trials, of which more than 1,300 had been treated for at least 48 weeks and more than 600 had been treated for at least 96 weeks.

Clinical pharmacology

Pharmacodynamics

- Mechanism of action

Emtricitabine is a nucleoside analogue that acts as an inhibitor of HIV reverse transcriptase. Emtricitabine has been shown to be specific for HIV-1, HIV-2 and HBV. EC_{50} values for HIV-1 and HIV-2 are from 0.0013 to 0.5 μM and 0.08 to 1.5 μM, respectively. Concentrations up to 100 μM emtricitabine had no effect on human mitochondrial function and morphology and emtricitabine 5'-triphosphate was a very weak inhibitor of human DNA polymerase α, β, γ, and ε. Additive or synergistic activity was shown for emtricitabine in *in-vitro* combinations with a range of other NRTIs

as well as with NNRTIs and HIV protease inhibitors (PIs). There is currently no clinical experience on the use of emtricitabine in combination with cytidine analogues and therefore combination therapy that includes either lamivudine or zalcitabine cannot be recommended.

In vivo, an association was found between virological failure during emtricitabine therapy and virus that has the M184V mutation. These viruses were shown to be phenotypically resistant to inhibition by emtricitabine and lamivudine but remained sensitive to inhibition by didanosine, zidovudine, stavudine, tenofovir, zalcitabine and abacavir (<3-fold change in EC_{50}). Genotypic analyses have been performed in the main clinical studies, which are presented under the discussion of clinical efficacy.

- Dynamic studies

The antiviral effect of emtricitabine and its relationship to the dose was assessed in two short-term, open label studies (FTC-101 and FTC-102) using emtricitabine monotherapy in HIV-infected subjects. These studies are further discussed under the section on dose-ranging studies.

Pharmacokinetics

The pharmacokinetics of emtricitabine was determined in a series of phase I, phase I/II and phase III studies in various population: HIV-negative healthy volunteers, HIV-negative subjects with normal or impaired renal function, HIV-infected adults and HIV-infected children from 4 months of age.

Emtricitabine concentrations in plasma, urine and other biological fluids have been determined using validated LC/MS methods.

Absorption and distribution

Emtricitabine was rapidly and extensively absorbed after oral administration with maximum peak plasma concentrations reached within 1-2 hours after dosing in fasting state.
In fasting and non-fasting HIV-infected subjects, C_{max} and AUC emtricitabine increased in a dose proportional fashion after single and multiple doses of 200 mg up to 1200 mg daily. C_{max} and AUC values after the 200 mg dose were of the same order in healthy volunteers and in HIV-infected subjects. The mean trough concentration was approximately 4-fold higher than the mean IC_{90} for emtricitabine.

Under fasting conditions, the absolute bioavailability of emtricitabine from the hard capsule (200 mg) was estimated to be 93% while that from the oral solution (10 mg/ml) was 75%, giving a relative bioavailability of the capsule *versus* oral solution of 124%. The reasons for this difference in bioavailability are unknown.

Administration of emtricitabine as 200 mg hard capsules with a high-fat meal did not affect systemic exposure ($AUC_{0\text{-}inf}$) of emtricitabine; therefore, Emtriva 200 mg hard capsules may be administered with or without food. The mean C_{max} and $AUC_{0\text{-}inf}$ for the 200 mg capsule formulation administered with a high-fat meal were decreased by approximately 29% and 10%, respectively, compared to administration in the fasted state. In addition, mean tmax was prolonged by approximately by 1.5 hours (1.1 to 2.6 hours). No study of the effect of food on absorption from the oral solution has been performed. However, pharmacokinetic data obtained in children showed that 6 mg/kg of emtricitabine administered daily as oral solution regardless of the food intake gave similar AUCs to those of adults after 200 mg daily as capsules. Therefore, as mentioned in the Summary of Product Characteristics, emtricitabine capsules and oral solution can be administered with or without food. The applicant however undertook to conduct a study to evaluate the effect of food on absorption of emtricitabine from the oral solution, the results of which will be provided post-authorisation.

The steady state apparent volume of distribution of emtricitabine after iv administration averaged 109 l (1.4 l/kg) suggesting that emtricitabine is widely distributed to both the intra- and extra-cellular fluid spaces. The mean plasma to blood concentration ratio was about 1.0. The semen to plasma concentration ratio was about 4, suggesting good penetration.

Plasma protein binding of emtricitabine *in vitro* was less than 4% and was independent of the dose. The intracellular half-life of emtricitabine 5'triphosphate was estimated to be $\geq$ 39 hrs. Saturation of intracellular levels of emtricitabine 5'-triphosphate correlated with a plateau of HIV-1 RNA suppression at 1.9 $\log_{10}$ at 200 mg per day.

Metabolism and elimination

The predominant radioactive component in plasma (almost all), urine (>82%) and faeces (almost all) was unchanged ^{14}C-emtricitabine. Thus, metabolism appeared to be a minor elimination pathway for emtricitabine. Metabolism in humans is similar to that in the monkeys and involves:
(1) oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers M1 and M2 (9% of dose), with M2 being predominant
(2) conjugation with glucuronic acid to form the 2'-O-glucuronide (M3) (4% of dose).

In in-vitro studies using pooled human liver microsomes, emtricitabine was not an inhibitor for human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4/5. One minor metabolite of emtricitabine (about 1%) was detected in cDNA-expressed CYP 3A4 incubations but was not formed by any other isoenzyme investigated (CYP 1A2, 2A6, 2B6, 2D6, 2E1, 2C8, 2C9 or 2C19). Emtricitabine did not show any inhibitory effect on UDP-GT as assessed by 7-hydroxycoumarin (a substrate of many isoforms of UDP-GT) glucuronidation. No glucuronidation of emtricitabine was observed in the presence and absence of an NADPH-generating system and uridine 5'-diphosphoglucuronic acid (UDPGA).

Approximately 69% of a 200 mg capsule dose and 55% of a 200 mg oral solution dose were recovered as unchanged drug in the urine over 48 hours, with most recovered during the first 12 hours. CL_R values for individual subjects were consistently greater than creatinine clearance values indicating net renal tubular secretion of emtricitabine. The plasma elimination half-life after 100 mg or 200 mg q.d. in HIV-infected subjects was approximately 10 hrs.

Special populations

Pooled data from single doses studies, which included 108 volunteers and 16 HIV infected subjects were used to assess the influence of demographic variables on the pharmacokinetics profile of emtricitabine. The mean AUC was higher in female subjects as compared to males, in subjects > 40 years as compared to subjects ≤ 40 years of age, in subjects with a body weight ≤ 75 kg as compared to subjects with a body weight > 75 kg as well as in subjects with a body surface area ≤ 1.91 m^2 as compared to subjects with a body surface area > 1.91 m^2. However the magnitude of the difference in emtricitabine pharmacokinetics parameters was <20 % and most commonly <10 %, and therefore it was considered unlikely that these differences would be of clinical significance.

No specific pharmacokinetics studies have been conducted in elderly patients.

Renal insufficiency

Pharmacokinetic parameters were determined following administration of a single dose of 200 mg emtricitabine to 30 non-HIV infected subjects with varying degrees of renal impairment according to baseline creatinine clearance. Groups were: > 80 ml/min as normal function; 50 – 80 ml/min as mild impairment; 30 – 49 ml/min as moderate impairment; < 30 ml/min as severe impairment; < 15 ml/min as functional anephric requiring haemodialysis. The mean emtricitabine exposure ± standard deviation increased from 11.8±2.9 µg.h/ml in subjects with normal renal impairment to 19.9±1.1, 25.0±5.7 and 34.0±2.1 µg.h/ml in patients with mild, moderate and severe renal impairment, respectively. In patients with ESRD requiring haemodialysis approximately 30% of the emtricitabine dose was recovered in dialysate over a 3-hour dialysis period started within 1.5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and a dialysate flow rate of approximately 600 ml/min).

A pharmacokinetic modeling and simulations of multiple dose emtricitabine plasma levels from the single dose pharmacokinetics supported a need for reductions in the daily dose or dose interval adjustments when creatinine clearance falls below 50 ml/min. Although persons with creatinine clearance in the range 50-80 ml/min will have slightly higher exposures than persons with normal renal function, it is not expected that this would have any major adverse effects on the safety profile of emtricitabine.
For the 200 mg hard capsule, dose interval adjustments have been recommended. Alternatively, patients with creatinine clearance < 50 ml/min may receive a reduced daily dose of emtricitabine administered as the oral solution. In both cases, the Summary of Product Characteristics highlights the lack of clinical safety or efficacy data to support these recommendations.

Hepatic insufficiency

There are no data in patients with hepatic impairment. Since emtricitabine is primarily excreted via renal route, no dosage adjustment is expected to be necessary.

HIV-HBV co-infected patients

Results from an open-label, dose escalation study in HBV patients with doses ranging from 25 mg to 300 mg emtricitabine daily for 8 weeks suggested that 200 mg emtricitabine gives similar exposure to emtricitabine as in HIV-infected patients.

Children

The pharmacokinetics of two single doses of emtricitabine (administered as the oral solution; 60 mg/m^2 and 120 mg/m^2 up to maximum of 200 mg) were evaluated in an open-label, non-randomised study in HIV-1 infected or potentially infected (*i.e.* born to HIV-infected mothers) infants, children and adolescents aged from 4 months to < 18 years. Children were divided into in five cohorts by age at the time of the first dose. After 120 mg/m^2 doses, $AUC_{0\text{-}inf}$ values were between 7.7 and 8.4 μg.h/ml which was similar to or slightly lower than the median $AUC_{0\text{-}inf}$ or $AUC_{0\text{-}24}$ values following single or multiple doses of 200 mg emtricitabine as capsules in adults. From these data it was projected that 6 mg/kg dose administered as the oral solution would provide AUC values similar to or higher than those following the 120 mg/m^2 dose in FTC-105. This 6 mg/kg dose was further evaluated in two studies in HIV-infected children (FTC-202 and 203) and pharmacokinetic data from these patients supported the recommendation for 6 mg/kg doses. Taking into account the lower bioavailability of emtricitabine from the oral solution, children may be dosed at 6 mg/kg/day up to 240 mg daily as the solution. Alternatively, children who weigh at least 33 kg may choose to switch to the capsules at any time as recommended in the Summary of Product Characteristics.

Interactions with other medicinal products

Since emtricitabine was a poor substrate for the human cytochrome P450 system *in vitro* and lacked inhibitory activity for the major cytochrome P450 isoenzymes, clinically significant interactions that involve CYP isoenzymes are not expected.

In an initial single dose study enrolling a small number of healthy volunteers (n = 6) who received emtricitabine (200 mg) co-administered with zidovudine (300 mg), the apparent clearance of zidovudine decreased with a 1.26 fold (26 %) increase in AUC and 1.7-fold (65%) increase in C_{max}.

A second multiple dose three-way cross over study was conducted in which 17 healthy volunteers received 7 days of each of 200 mg emtricitabine q.d., 300 mg zidovudine b.i.d. and both together. The AUC_{tau} and $C_{max,\ ss}$ of zidovudine increased by about 13% and 17%, respectively, and the AUC_{tau} and $C_{max,ss}$ of zidovudine glucuronide increased by about 6% and 9%, respectively. There was no significant pharmacokinetic interaction at the level of renal tubular secretion. These findings were reviewed in the light of results of study FTC-303, further described under the clinical efficacy section, in which the background regimen was stavudine or zidovudine plus an NNRTI or PI. The proportion of patients who took zidovudine during the study was 126/294 (43%) in the emtricitabine arm and

70/146 (48%) in the lamivudine arm. In this subset, emtricitabine and lamivudine had similar antiviral activity and there were no notable differences in the safety data. Therefore, the interaction noted was not thought to be of clinical significance.

There were no clinically significant pharmacokinetic interactions when emtricitabine was co-administered with indinavir, stavudine, or tenofovir disoproxil fumarate.

The bioavailability of emtricitabine and penciclovir (as famciclovir) were slightly less (7-9%) when co-administered. Nevertheless, the degree of difference in AUCs observed was not considered to be clinically significant.

It may be predicted that co-administration of 200 mg emtricitabine with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway.

Clinical efficacy

An overview of the clinical studies submitted to support the efficacy and safety of emtricitabine in HIV infected adults and children are displayed in table 1.

i. Main Studies in treatment naïve and experienced patients					
Study Type / No.	**Population/sites**	**Design**	**Objective**	**Emtricitabine Patients Planned/ Enrolled**	**Study Report**
FTC-301A Revised	Adult, HIV-1 infected, treatment-naïve North America, Latin America, Europe	Randomized, double-blind, controlled	Safety and efficacy equivalence to stavudine within a Triple Drug Combination Containing Didanosine Plus Efavirenz	250/286	48 weeks reported
FTC-302	Adult, HIV-1 infected, treatment-naïve South Africa	Randomized, double-blind, controlled	Safety and efficacy equivalence to lamivudine within a Triple Drug Combination	250/234	48W
FTC-303/ FTC-350	Adult, HIV-1 infected, lamivudine-experienced, stable HIV-1 RNA Patients on a Stable Triple Antiretroviral Therapy Regimen Containing Lamivudine, Stavudine or Zidovudine, and a Protease Inhibitor or Non-Nucleoside Reeverse Transcriptase Inhibitor /	Randomized, open-label, controlled, responders in FTC-303 roll over to FTC-350 (single arm FTC)	Safety and efficacy equivalence to lamivudine at 48 weeks in a switch setting, long-term safety and efficacy in rollover (FTC-350)	FTC-303 300/294 FTC-350 289 Total 419/368	48W FTC-303/ Safety Data for FTC-350
ii. Studies in children					
FTC-203	Paediatric (3 mo-17yrs), HIV-1 infected, treatment naïve and lamivudine experienced	Open-label experienced: switch lamivudine to emtricitabine Naïve: emtricitabine + stavudine + Lopinavir/ritonavir	Safety, PK, and antiviral activity in paediatric patients	80/83	Synopsis of ongoing study
FTC-202 (PACTG 1021)	Paediatric, HIV-1 infected, treatment-naïve	Open-label, single arm eFTC +ddI +EFVfor 48 weeks	Safety and efficacy in pediatric population w/HIV-1 infection	42/37	Draft interim report
Supportive studies					
ANRS 099/ ALIZE	Adult, HIV-1 infected, treatment-experienced, stable HIV-1 RNA 58 centres in France	Randomized, open-label, switch; rollover includes subjects rolling from non-emtricitabine arm to emtricitabine	Compare safety and efficacy between continuing on stable therapy and switch to emtricitabine, didanosine, efavirenz (all QD)	Original 175/178 Rollover 175/150 Total 350/328	48 weeks results presented at 10th Conference
FTC-201 (ANRS-091-MONTANA)	Adult, HIV-1 infected, treatment naïve	Open-label, single arm, QD regimen extended 4 years	Safety, efficacy of QD triple regimen emtricitabine, didanosine, efavirenz	40/40	Published findings only (96 weeks)
ACTG5015	HIV-1 infected, treatment- naïve C1:>13<30 yrs C2:>45 yrs	Open-label, single arm (emtricitabine + stavudine lopinavir/ritonavir), two age cohorts	Explore the basis of accelerated age associated HIV-disease progression	90/91	Synopsis of study status

Dose-response studies and main clinical studies

Dose response studies

FTC-101 was a dose escalation study to investigate the safety, pharmacokinetics and antiviral activity of multiple repeated doses of emtricitabine in HIV infected patients. The study was performed in 41 adult patients naïve to lamivudine and abacavir with plasma HIV RNA ≥ 5000 copies/ml and CD4 cell counts ≥ 200 cells/mm^3. Median changes in HIV-1 RNA from baseline to Day 15 increased with the dose and reached an apparent plateau at doses between 200 mg qd and 200 mg bid. Median viral suppression was 1.9 log_{10} at 200 mg q.d. and b.i.d. compared to 1.3, 1.5, and 1.7 log_{10} for the 25 mg b.i.d., 100 mg q.d. and 100 mg b.i.d. groups, respectively. There was a statistically significant correlation between the dose and the change in viral load from baseline while the correlation between dose and AAUCMB (average area under the time curve minus baseline) to Day 15 approached significance (p=0.055). The maximum AAUCMB was estimated to be 1.34 log_{10}.

In study FTC-102, emtricitabine monotherapy (at 25 mg, 100 mg and 200 mg q.d.) was compared with lamivudine monotherapy (at 150 mg b.i.d.) over 10 days. The study was performed in 4 cohorts of 20 adult HIV infected patients naïve to lamivudine and abacavir with CD4 cell counts ≥ 200 cells/mm^3 and HIV RNA ≥ 5000 to < 100,000 copies/ml. A dose response relationship was observed for viral suppression as analysed by AAUCMB through Day 12. There was a statistically significant difference between the emtricitabine 200 mg q.d. and the lamivudine groups with respect to AAUCMB through Days 11 and 12 (p = 0.04) with values of –0.98 log_{10} for lamivudine versus – 1.04 log_{10} for emtricitabine at day 11 and – 1.01 log_{10} and – 1.14 log_{10} at day 12. There was no statistically significant difference between 100 mg and 25 mg emtricitabine doses and lamivudine.

Relationship between plasma concentration and effect

Based on the parameter estimates obtained from the dose-response analysis using E_{max} modelling, the anti-HIV activity of emtricitabine was predicted to reach a plateau as dose increases, with little difference in the activity between the 200 mg and 400 mg doses. A dose of 200 mg per day was predicted to achieve close to 95% of the maximal antiviral activity with little additional (approximately 3%) activity observed at the 400 mg dose per day.

These results, along with the pharmacokinetic data and anti-viral activity of emtricitabine, supported the choice of 200 mg once daily as the recommended dose in the main clinical studies.

Main study(ies) (phase III = therapeutic confirmatory trials)

Studies in antiretroviral treatment-naïve adult patients: studies FTC-301A and 302

Description of the study

Study FTC-301A compared emtricitabine 200 mg q.d. with stavudine (30 or 40 mg b.i.d. by weight), each administered with both didanosine (enteric coated 250 mg or 400 mg q.d. by weight) and efavirenz (600 mg q.d.) in antiretroviral naïve adult patients.

Patients were stratified at entry according to HIV RNA 5-100,000 or >100,000 copies/ml and site of enrolment. The study was unblinded on the Data Safety Monitoring Board's recommendation following a planned interim analysis at week 24.

Study FTC-302 compared emtricitabine once daily to lamivudine twice daily when used with a background regimen containing stavudine and a NNRTI.

Patients were randomised (1:1 with respect to emtricitabine: lamivudine) to:
- Stratum 1(HIV RNA baseline ≥ 5,000 and ≤ 20,000 copies/ml) and Stratum 2 (HIV RNA baseline > 20,000 and ≤100,000 copies/ml) (n = 200): emtricitabine (200 mg q.d.) or lamivudine (150 mg b.i.d.) + stavudine (30 or 40 mg b.i.d. by weight) + nevirapine (200 mg q.d. for 14 days and then

200 mg b.i.d.)
- Stratum 3 (HIV RNA baseline > 100,000 copies/ml) (n = 50): emtricitabine (200 mg q.d. or lamivudine (150 mg b.i.d.) + stavudine (as above) + efavirenz (600 mg q.d.)
This differentiation of treatment by stratum was on FDA advice and was due to the absence of conclusive data to support the efficacy of nevirapine in patients with HIV-RNA >100,000 copies/ml.
When the last patient completed 48 weeks of treatment, all patients still on blinded study medication with ≤ 2000 copies/ml were offered continuation on an open label triple regimen.

Primary endpoints/assays

The primary assessment of efficacy was the proportion of randomised and treated patients with durable suppression of plasma HIV-1 RNA less than the limit of assay detection (LOD) through 48 weeks of study. In study FTC-301A, ≤ 50 copies/ml was the primary endpoint but both ≤ 50 and ≤ 400 copies/ml were considered co-primary endpoints in study FTC-302.

For efficacy evaluation in the pivotal studies, the following populations were defined:
- Intent-to-treat (ITT): All subjects randomised who receive at least one dose of study medication, regardless completion of study protocol; this was the primary population in the analyses of the two studies.
- As-treated population (ATR): all patients for whom no clear evidence was available of failure to take study medication and who had non-missing data at a given time point.
- All randomized population: all patients randomized, regardless of whether or not the study drug was actually taken or if the patient completed the planned duration of the study.
- Virological evaluable population: all patients having received at least one dose of study medication with a plasma HIV-RNA on or after week 12, while on prescribed treatment.

The following definitions of outcomes were used in both studies:

- *Loss of virological response* was defined as plasma HIV-1 RNA > 400 copies/ml on two consecutive measurements after achieving a plasma HIV-1 RNA level at or below 400 copies/ml while receiving the prescribed study medication.
- *Lack of virological response* was defined as failure to achieve plasma HIV-1 RNA ≤ 400 copies/ml by Week 12 (study FTC-301A) or at any time during the study (FTC-302).
- *Virological failure* was deemed to have occurred if the patient had either loss or lack of a virological response. In study FTC-302, virological failures were also sub-classified as being associated with resistance if lack or loss of response occurred with emergence of mutations corresponding to NRTI or NNRTI drugs within the regimen.
- *Tolerability failure* occurred when a patient had any adverse event that leads to permanent discontinuation of the blinded study drug.
- *Effectiveness failure* was defined as virological failure, death, clinical disease progression (*i.e.*, a development of a new CDC class C event), or premature treatment discontinuation (*i.e.*, due to tolerability failure, lost to follow-up, or other reasons).
- *Efficacy failure* was defined as virological failure, death, clinical disease progression (i.e., a development of a new CDC class C event), or treatment discontinuation due to the patient being lost to follow-up.

Statistical analysis

In study FTC-301A, non-inferiority was considered to have been demonstrated if the lower 95% stratum adjusted confidence interval around the difference between treatments in the proportions of patients with ≤ 50 copies/ml at week 24 was within -10%. Patients who discontinued the study or were lost to follow-up were considered failures (NC = F). However, patients who had missing data between were censored at that timepoint (i.e. excluded from the numerator and denominator).
In study FTC-302, non-inferiority was considered to have been demonstrated if the lower 95% confidence interval around the difference between the two treatments in the proportion of patients whose plasma HIV RNA was ≤ 400 copies/ml at Week 48 was within –12.5%. Patients who discontinued the study or were lost to follow-up were considered failures (NC = F).

RESULTS

Study populations/accountability of patients

Study FTC-301A

Up to week 24, there were no major differences between treatment groups with respect to premature discontinuations (89% completed 24 weeks of emtricitabine and 89% of stavudine). When the last patient completed 24 weeks (database cut-off), 244 (77%) of a potential 319 patients had completed 48 weeks on study, but rates were 81% for emtricitabine and 72% for stavudine. The difference was mainly due to discontinuations because of adverse events after week 24 (6% *versus* 12%) or virological failure (3% *versus* 9%).

The baseline characteristics were well balanced between the treatment groups. The majority of patients were male (85%) and Caucasian (52%) with a mean age of 36 years. The mean baseline HIV-RNA was 4.8 $\log_{10}$ copies/ml. Approximately 40 % of patients had baseline HIV-RNA > 100,000 copies/ml and the mean CD4 counts were 318 cells/mm^3. About 80 % of patients had no history of HIV related events.

Study FTC-302

Overall, 71% in the emtricitabine and 77% in the lamivudine group completed treatment up to week 48. Twenty patients in each treatment group withdrew due to virologic failure with genotypic evidence of resistance, and twenty-two patients in each treatment group withdrew due to adverse events prior to completing week 48.

Demographic characteristics were well balanced between treatment groups. Overall, 59% of patients were female, with 77 % of Black origin and a mean age of 33 years. The mean baseline HIV-RNA was 4.5 $\log_{10}$ copies/ml. Approximately 15% of patients had baseline HIV-RNA > 100,000 copies/ml and mean CD4 count of 389 cells/mm3. Approximately 82% were stratified to nevirapine and about 78% did not have any history of HIV related events.

Efficacy results

Study FTC-301A

The results for the primary efficacy endpoint at week 24 and week 48 (for those who had reached that timepoint at the time of the interim analysis) the differences between treatments were all statistically significant in favour of the emtricitabine group (table 2). The results for the secondary endpoints are presented in table 3.

Table 2: Primary Efficacy Endpoint at Interim analysis

ITT Population	**d4T (N=285)**	**FTC (N=286)**	**Difference (d4T-FTC)***	**95% CI***
At Week 24				
% ≤ 50 copies/ml (NC=F)	69.6	80.9	-11.3	(-18.0, -4.6)
Week 48 Evaluable Population	**d4T (N=163)**	**FTC (N=156)**	**Difference (d4T-FTC)***	**95% CI***
At Week 24				
% ≤ 50 copies/ml (NC=F)	66.5	80.0	-12.3	(-21.3, -3.3)
At Week 48				
% ≤ 50 copies/ml (NC=F)	55.6	72.9	-17.5	(-27.5, -7.5)

*All differences and CIs are stratum-adjusted. ; d4T = stavudine and FTC = emtricitabine

Table 3: Treatment Differences in Secondary Efficacy Endpoints at Interim analysis: ITT Population

Week 24 Endpoint	d4T (N=285)	FTC (N=286)	Difference (d4T-FTC)*	95% CI*
% ≤ 400 copies/ml (NC=F)	79.3	86.9	-6.8	(-12.6, -1.0)
Efficacy Failure[1] (%)	13.0	7.0	4.9	(0.4, 9.4)
KM probability of Efficacy Failure[1] (%)	14.0	7.2	6.8	(1.7, 11.9)
Confirmed Virologic Failure (%)	9.5	3.8	4.4	(1.1, 7.7)
KM probability of Virologic Failure (%)	10.3	3.8	6.6	(2.3, 10.9)
Effectiveness Failure[2] (%)	20.4	14.0	5.9	(0.2, 11.6)
KM probability of Effectiveness Failure[2] (%)	21.8	14.0	7.8	(1.5, 14.0)
Mean $CD4^+$ cell change from BL[3]	118.7	155.6	-30.1	(-54.2, -6.0)
Mean $CD4^+$ cell percent change from BL	5.1	7.5	-2.3	(-3.1, -1.5)

d4T = stavudine and FTC = emtricitabine
1 Week 24; defined as virologic failure, clinical disease progression, death or lost to follow-up.
2 Week 24; defined as virologic failure, clinical disease progression, death, premature treatment discontinuation due to any reason.
3 Units are cells/mm^3.
*Differences and CIs are not stratum-adjusted for KM probability analyses but are stratum-adjusted for all other secondary endpoints.

The results by individual strata (site of enrolment and baseline HIV RNA) supported these observations.

To assess the robustness of the primary efficacy analysis based on the ITT population, retrospective analyses (based on individual per protocol criteria and combined criteria) were performed (table 4). In each case, there was numerical superiority in favour of the emtricitabine treatment group and the 95% CI around the differences in proportion of patients reaching < 50 copies/ml indicated that non-inferiority was not demonstrated between treatments. Thus, the results of these additional analyses supported the conclusions that were drawn from the pre-defined primary analysis.

Table 4: retrospective analyses

	d4T (N=285)	FTC (N=286)	d4T-FTC [1]	95% CI
Per Protocol Analyses				
Evaluable[2]				
%< 50 cp/ml	195/243 (80.2%)	229/247 (92.7%)	-12.2%	-17.5, -6.8
%< 400 cp/ml	222/243 (91.4%)	245/247 (99.2%)	-6.5%	-10.2, -2.7
Duration[3]				
%< 50 cp/ml	195/252 (77.4%)	229/252 (90.9%)	-13.4%	-19.3, -7.6
%< 400 cp/ml	222/252 (88.1%)	245/251 (97.6%)	-5.8%	-9.8, -1.9
No Deviations[4]				
%< 50 cp/ml	176/252 (69.8%)	205/249 (82.3%)	-13.2%	-20.1, -6.3
%< 400 cp/ml	202/252 (80.2%)	220/248 (88.7%)	-7.7%	-13.6, -1.8
Overall Per Protocol[5]				
%< 50 cp/ml	176/221 (79.6%)	205/220 (93.2%)	-14.1%	-19.6, -8.6
%< 400 cp/ml	202/221 (91.4%)	220/220 (100%)	-6.9%	-10.3, -3.4
Sensitivity Analysis				
LOCF [6]				
%< 50 cp/ml	213/285 (74.7%)	241/286 (84.3%)	-9.7%	-15.7, -3.7
%< 400 cp/ml	249/285 (87.4%)	264/286 (92.3%)	-3.6%	-8.0, 0.8

d4T = stavudine and FTC = emtricitabine
[1] Statistical analyses have been adjusted for screening plasma HIV RNA and geographical region strata.
[2] Excludes subjects who have missing HIV-1 RNA data in Week 24 analysis window (Day 155 - Day 182).
[3] Excludes subjects who have permanently discontinued study for any reason before Week 24 (Day 155)
[4] Excludes subjects with any Clinically Important Protocol Deviation during the trial.
[5] Excludes subjects who do not meet all Per Protocol population definitions.
[6] Last plasma HIV-1 RNA observation carried forward to Week 24

A concern was raised with respect to the choice of a stavudine-based comparative regimen. However, it was noted that in this rapid evolving field, stavudine was the most prescribed compound in its class at the time of initiation of the study and the combination of stavudine with didanosine was a popular choice for the dual nucleoside analogue basis of therapy.

Genotypic analysis was performed retrospectively for isolates from patients classed as virological failures and data were obtained from 57/58 patients (16/17 emtricitabine and 41/41 stavudine) at baseline and at the time of virological failure. The 16 baseline isolates from emtricitabine patients showed that 6 (37.5%) entered the study with HIV RNA containing mutations at positions associated with NRTI or NNRTI resistance. In the stavudine group 13 (31.7%) patients entered the study with drug-associated mutations in the HIV-RT.
At the time of virological failure, 11/16 (68.8%) emtricitabine patients and 35/41 (85.4%) stavudine patients had virus that had developed at least one new mutation associated with antiretroviral therapy resistance.
An analysis of the differences in the rate of virological failure between treatments was performed after adjusting for baseline mutations. Patients in the stavudine arm who had TAMs at baseline were censored so that the analysis included all 17 emtricitabine failures but only 35 stavudine failures. The analysis confirmed that there was a lower incidence of virological failure in emtricitabine-treated patients (p = 0.0132). A sensitivity analysis was done in which virological failures in the stavudine arm that had a TAM (n=6) or a K103N (n=5) mutation at baseline and failures in the emtricitabine arm that had a K103N (n=3) mutation at baseline were censored. There was still a statistically significant difference in the incidence of virological failure in favour of emtricitabine (p = 0.0182).

Study FTC-302

In the ITT and as-treated populations, slightly lower proportions of patients in the emtricitabine treatment group achieved and maintained suppression of plasma HIV-1 RNA below 400 copies/ml through Week 48. Also, the stratum-adjusted 95% CI showed that the lower limit was > 12.5% for the ITT population. However, proportions at < 50 copies/ml were very similar between treatments and the lowest 95% CI was –12.6% (table 5).

Table 5: Primary Efficacy Endpoint at Week 48

Endpoint	FTC (N=234)	LAM (N=234)	Difference [2] (FTC – LAM)	95% CI [2]
% ≤ 400 copies/ml (NC=F)[1]	145/225 (64.4%)	164/230 (71.3%)	-6.9	-15.5, 1.6
% ≤ 400 copies/ml (As Treated)	145/168 (86.3%)	164/182 (90.1%)	-5.4	-11.8, 1.0
% ≤ 50 copies/ml (NC=F)[1]	136/226 (60.2%)	148/232 (63.8%)	-3.8	-12.6, 5.1
% ≤ 50 copies/ml (As Treated)	136/168 (81.0%)	148/182 (81.3%)	-1.6	-9.6, 6.3

FTC = emtricitabine; LAM = lamivudine; [1] Non-completer is considered "Failure" for this analysis, unless patient was censored from analysis as defined in statistical methods.
All differences and CIs are stratum-adjusted.; FTC = emtricitabine; LAM = lamivudine

The secondary analyses generally reflected the above findings in that there were small but consistent numerical differences between treatments that favoured the lamivudine regimen (table 6).

Table 6: secondary analyses

Endpoint	FTC (N=234)	LAM (N=234)	Difference (FTC – LAM)	95% CI
Efficacy Failure (%)	48/234 (20.5%)	45/234 (19.2%)	1.8	-5.2, 8.9
KM probability of Efficacy Failure[1]	22.3%	20.6%	1.7	-5.7, 9.1
Confirmed Virological Failure (%)	33/208 (15.9%)	23/208 (11.1%)	4.6	-1.7, 10.8
KM probability of Virological Failure	15.9%	11.2%	4.7	-1.5, 10.9
Confirmed Virological Failure With genotypic mutation (%)	20/208 (9.6%)	20/208 (9.6%)	1.0	-4.5, 6.5
Effectiveness Failure[3] (%)	89/234 (38.0%)	83/234 (35.5%)	2.6	-6.1, 11.3
KM probability of Effectiveness Failure[3]	38.1%	35.5%	2.6	-6.1, 11.4
CD4+ (Absolute) Mean Change from BL (LOCF)[4]	161.0	174.6	-16.0	-46.5, 14.4
CD4+ (Absolute) Mean Change from BL	191.2	205.8	-19.2	-54.0, 15.6

FTC = emtricitabine; LAM = lamivudine
[1] Defined as virologic failure, clinical disease progression, death or lost to follow-up.
[2] Includes mutations at M184I/V, G190A, K103N, Y181C, Y188C, V108I, K101, E138, V106.
[3] Defined as a premature treatment discontinuation due to any reason, clinical disease progression, or virologic failure.
[4] Last Observation Carried Forward analysis.
[5]All differences and CIs are stratum-adjusted except KM.

More of the virological failures in the lamivudine group had mutant virus at time of failure compared with those in the emtricitabine group (87% *versus* 61%).

Studies in antiretroviral experienced patients: FTC-303

Description of the study

Patients were randomised (2:1) to replacement of lamivudine 150 mg b.i.d. with emtricitabine 200 mg q.d. or to continuation with the existing lamivudine regimen.
Patients were to have been on a stable triple antiretroviral regimen containing lamivudine, an NRTI (stavudine or zidovudine), and a marketed PI or NNRTI for ≥ 12 weeks and were to have < 400 copies/ml at the time of the screening visit. Patients were stratified by < 50 or 50-400 copies/ml and by PI or NNRTI in the regimen.

Primary endpoints/assays

The primary assessment of efficacy was the proportion of randomised and treated patients with durable suppression of plasma HIV-1 RNA less than the limit of assay detection (≤ 400 copies/ml LOD) through 48 weeks of study. Patients who discontinued were considered as failures.

Statistical analysis

This was a non-inferiority study based on a 15% limit in the difference in proportions with < 400 copies/ml at week 48.

RESULTS

Study population/accountability of patients

Out of the randomised patients, 307 in emtricitabine and 152 lamivudine, 227 (77%) and 119 (82 %) completed the study as planned. Premature discontinuations were more frequent in the emtricitabine arm, mostly due to adverse events (4 %). The nature of these was quite diverse, they were generally of mild severity and their relationship to emtricitabine was uncertain.

Treatment groups were well balanced at baseline with respect to demographic variables. The mean viral load at baseline was 1.8 $\log_{10}$ copies/ml in each treatment group, with a range of 1.7 to 4 $\log_{10}$ copies/ml. All subjects entered the study with HIV-1 RNA ≤ 400 copies/ml, with the majority (86%) having HIV-1 RNA < 50 copies/ml. Previous exposure to antiretroviral drugs was not notably different between the two treatment arms. Nevirapine was the most frequent NNRTI (63% of subjects) and nelfinavir accounted for 88% of PI use.

Efficacy results

At Week 48, 73% in the emtricitabine group and 82% in the lamivudine group had plasma HIV-1 RNA ≤ 400 copies/ml. The stratum-adjusted difference between treatment group was –5.8 % with a lower bound of 95% CIs at -13.5 % meeting the protocol's pre-defined criteria for non-inferiority.

The findings at the ≤ 50 copies/ml cut-off were similar, with 68% emtricitabine and 75% lamivudine group patients at this level at week 48 in the stratum-adjusted and unadjusted analyses (see table 7).

Table 7: Secondary Efficacy Endpoints

Week 48 Endpoint	FTC (N=294)	LAM (N=146)	(FTC-LAM) Difference[1]	95% CI[1]
% HIV-1 RNA ≤ 50 copies/ml	67.8	74.8	-4.7	-13.0, 3.5
% Efficacy Failure[2]	10.2	10.3	-1.0	-5.9, 3.8
Probability of Efficacy Failure[3]	11.0	10.7	0.3	-6.0, 6.6
% Virological Failure[4]	7.8	7.5	-0.2	-4.1, 3.6
Probability of Virological Failure[3]	8.5	8.0	0.6	-5.1, 6.2
% Effectiveness Failure[5]	23.5	19.2	2.8	-4.7, 10.2
Probability of Effectiveness Failure[3]	23.8	19.2	4.6	-3.4, 12.7
% Progression of CDC Class C Event	0.7	1.4	0.9	-0.5, 2.3
Mean CD4+ cell change from Baseline	29	61	-30	-66, 5.8
Mean CD4+ cell % change from Baseline	2.5	1.7	0.81	0.0, 1.6

FTC = emtricitabine; LAM = lamivudine

[1] All differences and confidence intervals (CI) are stratum-adjusted with the exception of Kaplan-Meier probabilities of failure.

[2] Defined as virological failure, CDC Class C progression, death or lost to follow-up.

[3] Kaplan-Meier probability of failure at 48 Weeks. Associated confidence interval is not stratum-adjusted.

[4] Defined as HIV-1 RNA > 400 copies/ml on two consecutive evaluations

[5] Defined as virological failure, tolerability failure, CDC Class C progression, or lost to follow-up

A concern was raised since patients who switched from lamivudine to emtricitabine were less likely to maintain viral load less than 400 copies/ml and to achieve or maintain viral load less than 50 copies/ml after 48 weeks. These findings applied in the stratum adjusted and unadjusted analyses.

The results of the primary analysis might have favoured lamivudine due to the difference between treatment groups in discontinuations for reasons other than failure. Nevertheless, whereas the 13 patients that discontinued emtricitabine all had <50 copies/ml at the time of discontinuation, they were all at this level at baseline and 9/13 had discontinued before week 24 so that the last observation might not be very reliable.

Additional retrospective analyses were conducted to evaluate the impact of differences in withdrawals due to adverse events upon efficacy outcomes as follows (table 8):

Table 8: Efficacy Endpoint Analysis

Week 48 Endpoint	FTC (N=294)	LAM (N=146)	FTC-LAM [1]	95% CI
Responder Analysis				
% ≤ 400 cp/ml (NC=F) [2]	73.1%	81.7%	-5.8%	(-13.5, 1.8)
% ≤ 400 cp/ml ("as treated" at W48) [3]	97.6%	100%	-2.2%	(-4.4, 0.0)
% ≤ 400 cp/ml (LOCF at W48) [4]	92.2%	93.2%	-1.4%	(-5.4, 2.5)
FDA defined Responder [5]	76.5%	81.5%	-2.6%	(-10.0, 4.7)
Time to Virological Failure				
K-M Probability (TLOVR) [6]	23.5%	18.5%	5.0%	(-3.0, 12.9)
K-M Probability (protocol) [7]	8.5%	8.0%	0.6%	(-5.1, 6.2)

FTC = emtricitabine; LAM = lamivudine

[1] stratum adjusted difference between treatment arms according to randomisation strata for responder analyses. Difference and CIs are not stratum-adjusted for KM probability analysis.

[2] Protocol-defined analysis of plasma HIV-1 RNA that treats all patients that did not complete the trial as "failures"

[3] Per protocol analysis of plasma HIV-1 RNA using all evaluable patients at Week 48

[4] Per protocol analysis of plasma HIV-1 RNA using last plasma HIV-1 RNA observation carried forward to Week 48

[5] Provided to Triangle at pre-NDA meeting on July 3, 2002 as primary efficacy endpoint and consistent with the published Guidance for Industry entitled "Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval" October 2002

[6] FDA-defined TLOVR analysis (Addendum to FTC-303 CSR) – non-responders include discontinuations

[7] Protocol defined time to virological failure (HIV-1 RNA > 400 copies/ml on 2 consecutive visits).

The applicant submitted an efficacy analysis according to the Food and Drug Administration algorithm for time to loss of virologic response (TLOVR analysis), which is an acceptable endpoint when evaluating maintenance therapy, as mentioned in the CPMP Note for Guidance related to the clinical development of anti-HIV medicinal products. As shown in table 8, patients were numerically more likely to fail if they switched to emtricitabine but the lower 95% CI were actually within –10%.

It was considered that the additional analyses, particularly the very relevant analysis of TLVOR, suggested that the numerical differences between regimens might not be of major clinical significance.

Complete or at least partial (around M184) sequence analysis of baseline isolates was obtained for 23/34 virological failures (19/23 in the emtricitabine arm and 4/11 in the lamivudine arm). In the emtricitabine subset, the M184V/I mutation was present in 17/19 (89.5%) isolates at baseline. In the lamivudine subset, the M184V mutation was present in 3/4 (75%) isolates at baseline. Genotypic data were available for 33/34 patients at the time of virological failure. Two emtricitabine and the one-lamivudine patients with wild type virus at M184 at baseline had developed the M184V mutation.

Supportive studies

ANRS 099 (ALIZE)
This study compared the efficacy and safety of maintaining a PI-containing stable triple regimen versus changing to a combination of emtricitabine/didanosine/efavirenz administered once daily as in study 301A. Patients had < 400 copies/ml after 48 weeks on previous therapy, and were NNRTI-naïve. Randomisation was stratified according to whether patients had received NRTIs prior to HAART. The final report has not yet been published however the applicant provided preliminary data after 48 weeks post-switch, which were presented at the 10th Conference on Retroviruses and Opportunistic Infections in February 2003.

There were 355 patients randomised (177 PI-based and 178 emtricitabine-based) and the two treatment groups were well balanced with respect to baseline characteristics. By week 48, 21 and 18 patients in respective groups had discontinued treatment while four and five had discontinued follow-up.

The results are presented in table 9.

Table 9: Efficacy Outcome at Week 48 – ALIZE

Week 48 Endpoint	FTC	Maintenance Arm	FTC-Maintenance	95% CI
Number of Patients Randomized	178	177	-	-
% Virological Success [1]				
Intent-to-treat (Available Data)	163/174 (93.7%)	162/176 (92.1%)	1.6%	(-3.8%, 7.0%)
Intent-to-treat (Missing=Failure)	160/178 (89.9%)	155/177 (87.6%)	2.3%	(-4.3%, 8.9%)
% < 50 copies/ml				
Intent-to-treat (Centralised Virology Data)	159/168 (94.6%)	141/163 (86.5%)	8.1%	(1.9%, 14.4%)

FTC = emtricitabine; [1] Defined as no virological failure (HIV RNA ≥ 400 copies/ml on 2 consecutive evaluations) from baseline to week 48

The limited data suggested that patients who had responded to PI-based HAART without NNRTIs could be switched to a once daily regimen containing-emtricitabine without any detrimental effect on their virological response.

FTC-201 (ANRS-091; MONTANA STUDY)
This is an ongoing open-label study in which all patients receive once daily emtricitabine, efavirenz and didanosine. The study was extended to 4 years. There were 36/40 treatment-naive patients who had completed 96 weeks at which time 85% and 80% of patients had a viral load below 400 and 50 copies/ml, respectively.

ACTG 5015
As of May 2002, 72 treatment-naïve patients had at least 48 weeks of emtricitabine plus lopinavir/ritonavir and stavudine. In the week 24 ITT analyses, 60/91 (66%) had a viral load ≤ 50 copies/ml and 75/91 (82%) was at ≤ 200 copies/ml. For 53 patients evaluated at week 48, 39/53 (73.6%) had a viral load ≤ 50 copies/ml and 46/53 (86.8%) had a viral load ≤ 200 copies/ml.

Children

Limited data are available from two ongoing, open label studies in children:

- FTC-202 (PACTG-1021) enrolling 37 treatment-naïve HIV infected children (no prior antiretroviral therapy exposure or less than 56 days of perinatal prophylaxis) or children who have had 7 or less days of cumulative antiretroviral therapy who receive emtricitabine (6 mg/kg up to 200 mg daily), efavirenz and didanosine.

- FTC-203 enrolling 83 treatment-naïve HIV infected children (no prior antiretroviral therapy exposure or less than 56 days of perinatal prophylaxis) or children on a stable (≥ 90 days suppressive lamivudine containing ART regimen) who receive emtricitabine (6 mg/kg once daily; up to a maximum of 200 mg once daily) plus stavudine and lopinavir/ritonavir. On enrolment, treatment-experienced patients responding to a lamivudine-containing regimen are switched to emtricitabine with the same background therapy.

The main baseline characteristics for the two studies combined are presented in the table 10.

Table 10: baseline characteristics (FTC-202 an FTC-203)

Demographic Characteristic	ART Stratum		Overall (N = 114)
	Naïve (N = 83)	Experienced (N = 31)	
Age (yr)			
Mean (SE)	7.0 (0.5)	7.5 (0.7)	7.1 (0.4)
Range	0.3 – 17.9	1.1 – 15.9	0.3 – 17.9
Baseline Plasma HIV-1 RNA Viral Load (log_{10} copies/ml)			
Median	4.94	1.70	4.60
Baseline Absolute CD4+ Cell Count (cells/mm^3)			
Median	606	1,072	705
Emtricitabine Dosage Form at Study Entry (n, %)			
Solution	67 (80.7%)	21 (67.7%)	88 (77.2%)
Capsule	16 (19.3%)	10 (32.3%)	26 (22.8%)

The combined results for naïve and experienced populations from the two studies are presented at week 24 (using NC=F analysis) in table 11.

Table 11: Primary Endpoint at Week 24: Combined Studies FTC-202 and FTC-203 ITT Population

Endpoint (NC = F)	ART Stratum		Overall N = 114
	Naïve (N = 83)	Experienced (N = 31)	
≤ 400 copies/ml (n/N, %)	69/76 (90.8%)	26/31 (83.9%)	95/107 (88.8%)
≤ 50 copies/ml (n/N, %)	53/76 (69.7%)	22/31 (71.0%)	75/107 (70.1%)

The antiviral activity at week 24 was generally consistent across all age groups in both naïve and experienced children. The response rate at the 50 copies/ml cut-off was lower in the naïve infants aged 3 to 24 months (3/9; 33.3 %), which may be due to insufficient time on treatment for maturing immune function to overcome higher than average viral loads at study entry.

For both studies combined, the naïve subjects had a median increase in CD4+ cell count by +250 cells/mm^3 and in CD4% cells by +10%. These increases occurred regardless of age group or emtricitabine dosage form. In the experienced subjects, the decrease in median CD4+ cell count (-89 cells/mm^3) was thought to reflect the natural, age-related decline in CD4+ cells and the fact these children had already experienced virological success on their previous antiretroviral therapy.
The final results of these studies will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Co-Infection with HIV and HBV

In 100 HIV/HBV co-infected patients enrolled in the clinical studies, the emtricitabine-containing regimen for the treatment of HIV resulted in similar suppression of HBV DNA to that observed in a limited number of HBV-infected patients given emtricitabine 200 mg once daily. However, confirmatory studies of emtricitabine 200 mg q.d. for the treatment of HBV infected patients are still ongoing. Therefore, caution should be exercised when treating HIV/HBV co-infected patients as recommended in the Summary of Product Characteristics. The final results of the applicant's studies in HBV infected patients will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Clinical safety

Patient exposure

At the time of the submission of the application, 2 years safety data had already been reported for 237 HIV infected patients. An update of the safety was provided with the responses to the list of questions with a cut-off date of 31 March 2003, by which time 2136 HIV-infected adult patients had been exposed in the long-term adult studies, accounting for an estimated 2,855 subject years of exposure. Of the 2136 patients exposed to emtricitabine, 1348 (63%) were exposed for 48 weeks, 772 (36%) for ≥ 72 weeks and 607 (28%) for ≥ 96 weeks.

Discontinuation due to adverse events

The most frequent adverse events that led to study discontinuation in both treatment groups were AST increased (emtricitabine 2.0%, control 2.3%), ALT increased (emtricitabine 2.0%, control 2.3%), amylase increased (emtricitabine 0.6%, control 1.2%), and rash (FTC 0.7%, control 0.8%). Females discontinued due to adverse events (13.7% emtricitabine and 20.8% comparators) more often than males (7% and 9.9%, respectively).

Adverse events

In the two short-term monotherapy studies in HIV-infected adults, the most common adverse events considered emtricitabine-related in 101 patients treated with any dose level were nausea (16%), headache (12%), asthenia (12%), and increased appetite (6%). In study FTC-102, the overall incidence of treatment-related adverse events of any grade was comparable between groups (38% emtricitabine and 33% lamivudine), as were incidences of adverse events by body system and specific term.

For all adverse events reported in FTC-301A, -302 and -303, regardless of causality, 93% of emtricitabine patients and 97% of those in control groups had at least one adverse event. The most common adverse events in the emtricitabine group were infection (33% versus 43% with control); headache (22% versus 25% with control); diarrhoea (22% versus 27% with control); nausea (17% versus 19% with control); rash (17% versus 18% control); flu syndrome (15% versus 16% with control); pain (15% in both groups) and asthenia (14% in both groups).

Overall, females were notably more likely to report abdominal pain, headache, nausea and vomiting, raised liver function tests and respiratory and skin complaints than males. However, females on emtricitabine were not more likely to report these events than females on comparative therapy, with the exception of skin discoloration on emtricitabine (in females 8 % in emtricitabine and 1.5 % in comparators groups versus in males 1.9 % in emtricitabine versus 0.4 % comparators).

Table 12 shows the most common treatment-related adverse events in these three studies. In emtricitabine-treated patients the commonest were diarrhoea, headache, nausea, dizziness, abdominal pain, asthenia and rash. However, rates of these and other adverse events were similar between treatment groups. Incidences of adverse events were consistently higher in the first 6 months on therapy and then declined steadily over time.

Table 12: Treatment-Related Clinical Adverse Events (Grade 1-4) by Decreasing Order of Frequency Reported in ≥ 3% Emtricitabine-Treated Patients in Pooled Studies 301A, 302 and 303 (0-48 Weeks)

	Week 48 Pooled Safety Population (Controlled Studies)			
	Emtricitabine (N = 814)		Control (N = 665)	
	N	%	N	%
Total Reporting ≥ 1 Related* AE	**510**	**(62.7%)**	**429**	**(64.5%)**
Diarrhoea	114	14.0%	97	14.6%
Headache	83	10.2%	83	12.5%
Nausea	81	10.0%	86	12.9%
Dizziness	70	8.6%	79	11.9%
Abdominal Pain	64	7.9%	56	8.4%
Asthenia	64	7.9%	53	8.0%
Rash	58	7.1%	60	9.0%
Vomiting	47	5.8%	42	6.3%
Insomnia	39	4.8%	36	5.4%
AST (SGOT) increased	36	4.4%	43	6.5%
ALT (SGPT) increased	38	4.7%	44	6.6%
Dyspepsia	29	3.6%	26	3.9%
Pain	29	3.6%	25	3.8%
Abnormal dreams	26	3.2%	32	4.8%
Leukopenia	26	3.2%	16	2.4%

* includes events considered by the investigator to be remotely, possibly or probably related to study drug, or where study drug relationship data were missing.

Rashes

The rashes that occurred in adult HIV-infected patients included rash, pruritus, allergic reaction, angioedema, urticaria, maculopapular rash, vesiculobullous rash, pustular rash, Stevens-Johnson syndrome and erythema multiforme. The overall incidences of rash (all and related) for emtricitabine-containing regimens were similar to those for the various comparative regimens studied. Grade 3 or 4 rash, serious rash, or rash resulting in discontinuation of study drug each occurred in no more than 3% of emtricitabine-treated patients per study.

Rates of all rashes were higher in the two studies in treatment-naïve subjects (FTC-301A and FTC-302) in which a NNRTI was used in the regimens evaluated. Rates were lower in both treatment groups in the study in treatment-experienced subjects (FTC-303) in which 79% were receiving a protease inhibitor as part of the combination regimen.

The two cases of Stevens-Johnson syndrome in the emtricitabine group were of onset around 3 weeks into therapy, occurred in the nevirapine stratum and were considered unrelated to emtricitabine. The single case of erythema multiforme (also in the nevirapine stratum) had an onset at three weeks and was also considered to be unrelated to emtricitabine.

Fat distribution disorders

The main phase III studies did not collect data regarding fat distribution disorders so that the only information comes from the adverse event database and therefore must be viewed with caution. Overall lipodystrophy was seen in 26/814 (3%) patients treated with emtricitabine compared with 27/665 (4%) in the control groups. The class statement related to the risk of lipodystrophy reported with the use of antiretroviral therapy has been included in the Summary of Product Characteristics.

Lactic acidosis, pancreatitis, peripheral neuropathy and central nervous system disorders

The three cases of lactic acidosis reported in emtricitabine-treated patients in major trials were also taking stavudine. The class statement related to the risk of developing lactic acidosis reported with the use of nucleoside analogues has been included in the Summary of Product Characteristics.

There were no serious reports of pancreatitis, peripheral neuropathy or headache in emtricitabine-treated patients in the controlled studies. In the larger safety update population, the numbers of serious reports of these events were four of pancreatitis, one headache, and no cases of peripheral neuritis. There have been two serious reports of psychosis and single serious reports of convulsion, depression, emotional lability, meningitis and psychotic depression, most of which were not considered to be related to emtricitabine.

Infections

The incidences of infections that were reported as adverse events in treatment-naïve HIV-infected patients in studies FTC-301A and FTC-302 were similar in emtricitabine and comparator groups (33.3 % emtricitabine versus 32.5 % comparator in study FTC-301A and 42 % emtricitabine versus 50 % comparator in study FTC-302). Most of these adverse events (81-83%) were upper respiratory infections termed as 'common cold', 'cold', 'head cold' etc. Lower respiratory tract infections coded to 'infection' accounted for only 3% to 5% of the total. The majority was recorded as being of mild or moderate severity.

Serious adverse events (SAEs) and deaths

As of the cut-off date, 24 emtricitabine-treated patients had died. In the controlled, long-term studies in HIV-infected adults 4/1010 (0.4%) emtricitabine-treated patients and 10/861 (1.2%) patients in comparator treatment arms died. In uncontrolled long-term studies in adults the death incidence was 20/1670 (1.2%). Overall, the death rate in emtricitabine-treated patients across both controlled and uncontrolled studies was low 24/2465 (0.97%). Most of the deaths in emtricitabine patients were considered unrelated to emtricitabine and were mainly consistent with HIV-associated complications. In addition, one full-term infant (HIV positive) that was born to a female in study FTC-302 died approximately 7.5 weeks after delivery. The cause of death appears to have been septicaemia and HIV infection.

There were 93 (11.4%) emtricitabine patients who reported SAEs compared with 98 (14.7%) in the combined control group. SAEs reported in ≥ 1% of patients in the emtricitabine group were AST increased (emtricitabine 2.2%, control 1.1%), ALT increased (2.5%, control 3.0%) and pneumonia (1.5%, control 1.1%). All emtricitabine-treated patients with SAEs of kidney calculus in controlled studies were on indinavir concomitantly. Treatment-related SAEs included increased ALT, increased AST, hepatitis, and cellulitis.

Laboratory findings

Table 13 shows all grade 3 /4 laboratory abnormalities in the three main studies. The most common grade 3 / 4 laboratory abnormalities in emtricitabine patients were increases in creatine kinase, triglycerides, and ALT and AST.

Table 13: Grade 3 / 4 Laboratory Abnormalities in ≥ 1% Emtricitabine-Treated Patients in Pooled Studies 301A, 302 and 303 (0-48 Weeks)

	Week 48 Pooled Safety Population (Controlled Studies)			
	Emtricitabine (N = 814)		**Control (N = 665)**	
	N	**%**	**N**	**%**
Total With at Least 1 Abnormality ≥ grade 3 severity	**244**	**30.0%**	**211**	**31.7%**
Creatine kinase	83	10.2%	68	10.2%
Triglycerides	56	6.9%	30	4.5%
AST (SGOT)	44	5.4%	45	6.8%
ALT (SGPT)	43	5.3%	50	7.5%
Neutrophils	36	4.4%	31	4.7%
Serum Amylase	23	2.8%	37	5.6%
Serum glucose (increased)	14	1.7%	8	1.2%
Serum lipase	11	1.4%	9	1.4%
Total bilirubin	9	1.1%	12	1.8%
Pancreatic amylase	8	1.0%	7	1.1%

Grade 4 abnormalities included elevations in CPK, ALT, AST and triglycerides. Generally, incidences of Grade 3 or 4 abnormalities were higher in the first 6 months and declined slightly over time. Similar findings applied in the uncontrolled studies.

In FTC-302, the overall rates of increases in ALT and AST were 13-19% per treatment group. In fact, there were 66/385 (17%) patients in the nevirapine stratum reported with some degree of hepatotoxicity, of which 37 had been randomised to lamivudine (19%) and 29 to emtricitabine (15%). The sub-analyses reported showed that there was no excess of abnormalities in the emtricitabine group.

Special populations

HIV/HBV co-infected patients in emtricitabine and comparator groups had a higher incidence of Grade 3 or 4 ALT and AST elevations compared with HBsAg negative patients. However, there were no notable differences between treatment groups in either sub-population.

Caution should be exercised when emtricitabine is used in co-infected HIV-HBV patients as mentioned in the SPC.
In HCV/HIV co-infected patients, Grade 3 or 4 elevations in ALT or AST among emtricitabine-treated HCV+ patients were similar in incidence to that observed among HCV+ patients in the control treatment groups. Co-infected patients had a higher incidence of Grade 3 or 4 ALT and AST elevations.

Children

Data were available from FTC-203 and more limited data from FTC-202. At the cut-off dates, 120 subjects ≤ 21 years had been enrolled, of which 114 were < 18 years of age at baseline and had taken emtricitabine for a median of 36.1 weeks.

No deaths had been reported among children but there had been 22 SAEs in 17 subjects. In treatment-naïve subjects, the most common SAE was pneumonia, with six events in five subjects that were all assessed as unrelated to emtricitabine. Four subjects experienced adverse events that resulted in the permanent discontinuation of study treatment. These were two cases of rash and one of each of pancreatitis and anaemia (three were reported as SAEs) that were assessed as possibly and probably related to emtricitabine or, at least, to study treatment.

The overall incidence of adverse events of at least moderate severity was similar in treatment-naive subjects (37.3%) and treatment-experienced subjects (35.5%). Eight subjects had at least one Grade 3 (severe) or Grade 4 (potentially life-threatening) adverse event (three treatment-naïve and five treatment-experienced subjects). These included cases of pneumonia, sinusitis, gastroenteritis, leucopenia, anaemia, cellulitis and tooth caries.

The overall incidence of emtricitabine-related adverse events (all grades) was markedly higher in treatment-naïve subjects (54.9%) than in treatment-experienced subjects (12.9%). In treatment-naïve subjects, the most frequent (≥ 5%) emtricitabine-related adverse events were skin discoloration (39.2%), vomiting (17.6%), and nausea (5.9%) compared with leucopenia and anaemia in two (6.5%) experienced subjects. Skin discoloration was usually reported as hyperpigmentation (which in all cases was asymptomatic), mainly affecting the palms of the hands and/or the soles of the feet. This was assessed as being mild in severity and (with one exception) occurred in persons classed as black. This has been reported in HIV-infected adults and HBV-infected adults. It is thought that this is similar to changes in skin and nail pigmentation reported in black patients treated with zidovudine.

Almost all (97.6%) subjects had at least one treatment-emergent laboratory abnormality but < 5% had a Grade 3 or Grade 4 abnormality and only one subject with Grade 3 decreased haemoglobin discontinued due to these findings.

Pregnancies

Despite the measures as laid down in the protocols, 79 pregnancies occurred in 77 women (53 on emtricitabine), mostly in South Africa. There has been no excess of spontaneous abortions and no birth defects have been reported.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

The active substance is well characterised and documented. The pharmaceutical forms selected are adequate taken into account the properties and stability of the active substance. The excipients are commonly used in this kind of formulations and the packaging materials are well documented. The manufacturing processes enhance to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

Preclinical pharmacology and toxicology

Emtricitabine, which is an inhibitor of the HIV reverse transcriptase, presents an antiviral activity both *in vitro* and *in vivo* against laboratory and clinical isolates compatible with a potential clinical use for the treatment of HIV infection. The general pharmacology studies showed no treatment related adverse effects at systemic exposure levels much higher than those anticipated in patients at the recommended clinical dose. HIV-1 resistance, as observed *in vitro* and in HIV-1 infected patients to emtricitabine develops as the result of changes at codon 184 causing the methionine to be changed to a valine of the HIV reverse transcriptase. Emtricitabine resistant viruses were cross-resistant to lamivudine but remained sensitive to other NRTIs, NNRTIs and PIs. Viruses resistant to zidovudine, zalcitabine, didanosine and NNRTIs remained sensitive to emtricitabine.

The pharmacokinetics profile determined in mice, rats and monkeys showed that emtricitabine is rapidly absorbed after oral administration, widely distributed, and is eliminated primarily by renal excretion as unchanged compound.

Overall, the toxicology programme showed that emtricitabine has a low toxicity potential. Treatment effects in the repeated dose toxicity studies were limited to high doses only, which provided systemic exposure levels much higher than those expected in humans at the clinical doses, and primarily consisted of changes in the red cells parameters, considered as mild regenerative anaemia. There was no evidence of toxicity to reproduction neither in mice, rats or rabbits. Emtricitabine was not genotoxic. Final results from the carcinogenicity studies are not yet available, but this was justified and in view of the benefit/risk ratio, the CPMP considered a marketing authorisation could be granted prior the availability of these results. However the applicant undertook to submit the final results as part of the follow-up measures to be fulfilled post-authorisation.

Efficacy

The relationship between the dose and the antiviral effect of emtricitabine was investigated in two short-term monotherapy studies.

The dose of emtricitabine selected for the main clinical studies, 200 mg once daily, has been reasonably justified. Studies suggested that emtricitabine might be about 20 % more bioavailable from the capsule than from the oral solution.

The pharmacokinetics profile of emtricitabine was well defined and relevant information has been included in the Summary of Product Characteristics. Overall, after oral administration, emtricitabine is rapidly and extensively absorbed and widely distributed. The binding to plasma protein is very low. There is limited metabolism and emtricitabine is primary excreted via renal route as unchanged drug. Exposure to emtricitabine is significantly increased in patients with renal impairment. Daily dose reduction using the oral solution or dose interval adjustment using the capsules is required when creatinine clearance is below 50 ml/min, as recommended in the Summary of Product Characteristics.

Data in infants, children and adolescents (4 months to 18 years) showed that administration of 6 mg/kg emtricitabine as the oral solution (up to a maximum of 240 mg once daily) gives similar exposure as in

adults dosed with one 200 mg hard capsule daily. Due to the difference of bioavailability between the hard capsule and the oral solution, one 200 mg capsule should provide similar plasma levels to 240 mg emtricitabine administered as the oral solution.

Treatment-naïve subjects
Study FTC-301A showed a clear advantage of a 200 mg q.d. regimen of emtricitabine compared with stavudine when administered in combination with once daily didanosine and efavirenz, with an overall proportion of patients with plasma HIV RNA below the limit of quantification (50 copies/ml) in the ITT population (NC = F) population of 80.9 % at 24 weeks (69.6 % in the stavudine arm) and persisting at 48 weeks (72.9 % against 55.6 % in the stavudine arm).
In contrast, study FTC-302 showed that emtricitabine plus stavudine and either nevirapine or efavirenz was generally numerically inferior to similar lamivudine regimens. However, similar proportions of patients achieved a viral load suppression of ≤ 50 copies/ml (60.2 % in the emtricitabine arm versus 63.8 % in the lamivudine arm, ITT population with NC=F)) and by-stratum tabulations demonstrated no numerical inferiority for emtricitabine in the proportions reaching ≤ 50 copies/ml or in the rate of efficacy failure in the two strata with the higher baseline HIV RNA loads. Overall, the data supported the use of emtricitabine 200 mg q.d. for initial therapy for treatment naïve adult patients and suggested that efficacy might be particularly good when emtricitabine is combined with didanosine and efavirenz.

Treatment-experienced patients
The design of study FTC-303, in which patients still responding to a lamivudine-containing regimen were randomised to continue or to supplant lamivudine with emtricitabine while continuing on other compounds as before, was not inappropriate given the virological activity and nature of emtricitabine. In the primary analysis as planned, it appeared that patients who switched from lamivudine to emtricitabine were less likely to maintain HIV RNA ≤ 400 copies/ml (73 % versus 82 % in the lamivudine arm) and to achieve / maintain HIV RNA ≤ 50 copies/ml after 48 weeks (68 % versus 75 % in the lamivudine arm) (lower 95 % around the differences for these parameters were –13.5 % and –13%, respectively). However, several retrospective analyses, included the time to loss of virological response (TLOVR analysis) were submitted to support the non-inferiority of emtricitabine compared to lamivudine. While the TLOVR analysis showed that patients were numerically more likely to fail if they switched to emtricitabine, the lower 95% CI was within –10%. Among the additional analyses, the "as treated" population and the LOCF approach showed very similar response rates at the < 400 copies/ml level, with lower 95% CI within –6%.

The findings from ANRS-099 [ALIZE], where patients with stable suppression of HIV-1 RNA either continued on PI-based HAART or replaced the entire regimen with once daily HAART containing emtricitabine further support the efficacy of emtricitabine when used as part of an entirely once daily HAART regimen. In both treatment arms a high proportion of patients maintained suppression of HIV RNA (< 400 copies/ml) for 48 weeks (94% and 92% for the emtricitabine and maintenance groups, respectively – ITT available data). The treatment difference of –1.6% with a 95% confidence interval of –3.8%, 7.0%, supports the non-inferiority of the once daily emtricitabine regimen to the PI-based regimen.

There is no clinical experience of the use of emtricitabine in patients who are failing their current regimen or who have failed multiple regimens.

Children
The results from the two ongoing clinical studies in children (> 4 months to 18 years) satisfactorily demonstrated the efficacy of emtricitabine when given at 6 mg/kg/day as oral solution or as 200 mg q.d. as capsules in combination with other ART. After 24 weeks with stable virological control treatment, 90.8 % of naïve patients (69/76) and 83.9% of treatment-experienced children had achieved or maintained suppression of their HIV-1 RNA below ≤ 400 copies/ml. In addition, 69.7% of naïve patients (53/76) and 71% of treatment-experienced children (22/31) also achieved or maintained ≤ 50 copies/ml. The final results will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Safety

The most common emtricitabine-related adverse events were very much as expected from a NRTI that is structurally related to lamivudine. Nausea, diarrhoea, headache, asthenia, rashes and dizziness were all very commonly or at least commonly reported in several studies *i.e.* in conjunction with several different treatment regimens. For the most part, the incidences of adverse events declined with time. In part, this likely reflects withdrawals due to events although; given the withdrawal rates, there must also be an element of patients becoming more tolerant (or less likely to report) the more minor adverse events over time.

Among the events of special interest, emtricitabine *per se* does not appear to be very likely to trigger clinically significant anaemia, hyperlactataemia or pancreatitis and seems no more likely than lamivudine to contribute to the overall incidence of peripheral neuropathy.

The data in children did not suggest other potential adverse events than those observed in adults.

Two years' safety data were reported for 607 HIV-infected adult patients in this application. This number was considered to be sufficient to meet the requirements of the CPMP Note for Guidance on the clinical development of medicinal products for treatment of HIV infection (CPMP/EWP/633/02). However the applicant undertook to provide proposals for pro-active post-marketing assessments of safety in accordance with the requirements stated in the CPMP's Note for Guidance. These requirements include the need to conduct long-term post-marketing studies, as well as participation in, or sponsoring of, pharmaco-epidemiological studies that may be appropriate to the assessment of the long-term safety of emtricitabine.

Benefit/risk assessment and recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus decision that the benefit/risk profile of Emtriva 200 mg hard capsules and 10 mg/ml oral solution was favourable in the treatment of HIV-1 infection and therefore recommended the granting of the marketing authorisation in the following indication:

> "Emtriva is indicated for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents.
> This indication is based on studies in treatment-naïve patients and treatment-experienced patients with stable virological control. There is no experience of the use of Emtriva in patients who are failing their current regimen or who have failed multiple regimens.
> When deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate."