European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

INTELENCE

International Nonproprietary Name: etravirine

Procedure No. EMEA/H/C/000900

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 26 July 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for INTELENCE, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 14 December 2006.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication: "[INVENTED NAME], in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, including those with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance".

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 27 July 2005 and 18 October 2006. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:
An application for marketing authorisation for etravirine in the United States was pending at time of submission of the application to the EMEA.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis
Co-Rapporteur: Beatriz Silva Lima

1.2 Steps taken for the assessment of the product

- Accelerated Assessment procedure was not accepted by the CHMP on 19 July 2007.
- The application was received by the EMEA on 26 July 2007.
- The procedure started on 15 August 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2007.
- During the meeting on 10-13 December 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 13 December 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 March 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 May 2008.
- During the CHMP meeting on 27-30 May 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 4 June 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 16 June 2008.

- During the CHMP meeting on 23-26 June 2008 it was considered no longer necessary that outstanding issues are addressed by the applicant during an oral explanation in front of the CHMP.
- During the meeting on 23-26 June 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to INTELENCE on 26 June 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Infection with human immunodeficiency virus (HIV) and the resulting Acquired Immunodeficiency Syndrome (AIDS) are having significant human impact. As of December 2007, an estimated 33.2 million people worldwide, 30.8 million adults and adolescents and 2.5 million children, were living with HIV/AIDS. Approximately 50% of adults living with HIV/AIDS are women. An estimated 2.5 million new HIV infections and 2.1 million AIDS-related deaths occurred worldwide during 2007.

The advent of combination therapy for HIV infection in 1996 has had a significant impact on the natural history of HIV infection, with substantial decreases in HIV-related morbidity, mortality and use of health resources in regions of the world where an effective treatment intervention could be implemented. Further improvements in therapy and outcome have been challenged by the emergence of viral resistance to the antiretroviral (ARV) compounds currently marketed. Resistance to these ARV compounds has been, and is, a major reason for therapy failure and resistant virus has been reported in both treatment naive and treatment-experienced patients, often severely limiting the treatment options available. As a result, development of new, potent, safe and well tolerated ARV compounds with different and improved resistance profiles is needed for the increasing numbers of patients infected with multi-drug resistant HIV.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) play an important role and are widely used in the treatment of HIV infection, most commonly in first line therapy. However, the effectiveness of the current NNRTIs in later-line therapy is limited by a low genetic barrier to the development of resistance, which allows the selection of virus with reduced susceptibility and extensive NNRTI cross-resistance. Single mutations in the reverse transcriptase (RT) gene can lead to substantial reductions in susceptibility, often to all available inhibitors within the class. This broad cross-resistance within the class limits the sequential use after virologic failure of currently marketed NNRTIs. Also, therapeutic options with current NNRTIs are limited by side effects such as rash, central nervous system symptoms and hepatotoxicity. New agents with improved tolerability profiles and/or activity against NNRTI-resistant isolates would therefore offer new treatment options for treatment-experienced patients as well as those with transmitted (primary) NNRTI resistance.

Etravirine is a compound of the NNRTI class, thus sharing the common mechanism of action, for which effectiveness in viral strains which are resistant to other drugs in the class is claimed, thus allowing for the composition of salvage combination ART for HIV-infected subjects with previous exposure and documented resistance to other drugs in the class.

A so-called full application for marketing authorisation has been submitted, i.e. a complete and independent/stand-alone Marketing Authorisation Application. The applicant did request an accelerated assessment of the application, however the CHMP did not accept this request as it was not possible to assume that the product will be of major public health interest particularly from the viewpoint of therapeutic innovation. Etravirine could be expected to represent some advantages over other existing NNRTIs in view of its higher genetic barrier. Nevertheless, as it is not a representative of a new pharmacological class, the criteria for accelerated assessment were not considered to be met.

Subject to the applicant's application was a conditional marketing authorisation according to Article 14(7) of Regulation (EC) No 726/2004 in conjunction with Commission Regulation (EC) 507/2006. Based on the assessment the CHMP concluded that the application meets the criteria for conditional marketing authorisation, for the following reasons:

- Etravirine is indicated for the treatment of HIV-1 infection, which is a life threatening condition, therefore the application, being made under Article 3(1) of Regulation (EC) 726/2004, is in the scope of conditional marketing authorisation according to the Article 2(1) of Regulation (EC) 507/2006.
- Based on the available data and particularly the 24-week data from the two pivotal trials (DUET-1 and DUET-2) the risk-benefit balance is considered positive as these studies have shown that etravirine is able to provide an adequate virologic response in antiretroviral experienced patients with viral strains harbouring NNRTI resistance. Additional clinical data is needed to further substantiate the durability of virologic response and the use in combination with protease inhibitors other than darunavir/ritonavir, respectively. It is considered that the applicant will be in a position to provide these data so that eventually the data package will become comprehensive. Although not representing a new pharmacological class, etravirine does answer an unmet medical need in antiretroviral experienced HIV-infected patients with limited therapeutic options, insofar as it represents an additional tool for controlling the viral replication in patients harbouring multi-resistant strains. The pharmacological properties of etravirine make it an important antiretroviral treatment option in addition to recently approved compounds representing new classes of antiretroviral medicinal products. From a public health perspective the benefit of allowing etravirine to be marketed without undue delay may outweigh the risks inherent in the fact that additional data are still required. The requirements for a conditional marketing authorisation according to the Article 4(1) of Regulation (EC) 507/2006 are therefore met.

INTELENCE is available in tablets containing 100 mg etravirine. The recommended dose in adults is 200 mg (two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal.

The claimed indication at time of application read as follows: "[INVENTED NAME], in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, including those with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance."

The approved indication is:

> "INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients (see sections 4.4, 4.5 and 5.1).
>
> This indication is based on week 24 analyses from 2 randomised, double-blind, placebo-controlled Phase III trials in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, where INTELENCE was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir (see section 5.1)."

2.2 Quality aspects

Introduction

The medicinal product INTELENCE is presented as white to off-white, oval tablets containing 100 mg of etravirine. The active ingredient is present in an amorphous form. Other ingredients include hypromellose, ethanol, methylene chloride, colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, lactose monohydrate and microcrystalline cellulose.

The tablets are packaged in white, high-density polyethylene bottles with child-resistant, polypropylene closures lined with an induction seal. Silica gel pouches are added as desiccant.

Active Substance

The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. It is a white to slightly yellowish brown powder and is classified as a BCS Class IV compound (i.e., a low aqueous solubility irrespective of pH, and low to intermediate permeability). Etravirine may exist in two highly crystalline polymorphs. During production one polymorph has been consistently produced and the crystallization of this polymorph is under control. The polymorphism is not considered as critical for the efficacy of the product.

The chemical structure of etravirine has been confirmed using analytical data by elemental analysis, IR absorption spectroscopy, UV absorption spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy and mass spectrometry. All data are consistent with the proposed structure.

- Manufacture

Etravirine is manufactured from two starting materials by a three steps process. A purification is performed at each step. The three steps have an impact on critical quality attributes of the final etravirine drug substance and thus, are critical steps of the synthesis. Validation of the manufacturing process has been completed for three batches of the drug substance.

Appropriate specifications have been adopted for the starting materials, solvents, reagents and intermediates. All relevant impurities have been appropriately discussed and characterized. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

Stability studies have shown that etravirine is a stable compound and no degradation impurities have been detected under the tested storage conditions.

- Specification

The active substance specification include appropriate tests for appearance, identifications (HPLC and IR spectra), organic impurities, assay, residual solvents, heavy metals, residue on ignition and water. The impurity limits are acceptable and there is no concern in relation with safety or efficacy. The batch analysis data support the proposed acceptance limits.

- Stability

Stability studies have been performed in accordance with the ICH requirements. The results of long-term and accelerated stability studies show that etravirine drug substance is chemically and physically stable when stored for up to 24 months at 25ºC/60% RH and 30ºC/65% RH or for up to 6 months at 40ºC/75% RH. The stability data justify the proposed retest period without special storage conditions.

Medicinal Product

- Pharmaceutical Development

As etravirine is a compound with low aqueous solubility, the manufacturer improved the aqueous solubility, and as such also the bioavailability, by modifying the physical state of the drug (to the amorphous state) by means of the solid dispersion technology. During development of the formulation, several manufacturing techniques have been compared in order to improve the bioavailability and reduce tablet size at the same time. Clinical trials have shown that better bioavailability was obtained by using tablets manufactured from spray-dried material. Therefore, spray drying was selected as the preferred manufacturing technique of etravirine solid dispersions. In addition, formulation studies have been performed to identify an adequate stabilizer for the active

substance in solid dispersions.

- Manufacture of the Product

The manufacturing process starts with a spray-drying process in order to form the amorphous state of etravirine. After spray drying and mixing the spray-dried powder with various inactive ingredients, which are typical for an immediate release tablet formulation, the final solid dosage form was obtained through compaction and compression. The excipients used in the formulation are compendial ones, only lactose is from animal origin but for this excipient no TSE risk is expected. A BSE/TSE compliance statement from the lactose monohydrate supplier is provided.

All critical process parameters have been identified and controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the in-process and finished product specifications.

- Product Specification

The proposed specifications for the finished product at release are classical for this pharmaceutical form and include tests for identification, dissolution, uniformity of dosage units, water content and assay and related compounds by liquid chromatography. All methods have been validated according to the state of the art. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled.

- Stability of the Product

Stability studies were carried out according to the ICH requirements on three batches of the final commercial formulation. Twenty four months of stability data are provided for the 100 mg tablets lots stored at 25ºC/60%RH and 30ºC/75%RH and six months of stability data are provided for the 100 mg tablets stored at 40ºC/75%RH. The parameters tested include appearance, assay, chromatographic purity, water content, crystallinity, dissolution, and microbiological purity. The analytical methods were identical to the methods used for release and are stability indicating.

Additionally, stability studies have been performed under stress conditions (photostability study at 50ºC). In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC. No special storage conditions are required. In addition to this, also an in-use stability study was performed on 1 batch to support the daily use by the patient.

Discussion on chemical, pharmaceutical and biological aspects

The quality of INTELENCE is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. It is a poorly soluble substance that has been formulated as a solid dispersion before tabletting in order to overcome the solubility issues and to improve the bioavailability.

The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. At the time of the Opinion no quality issues remained unresolved.

2.3 Non-clinical aspects

Introduction

A comprehensive nonclinical programme was conducted to evaluate pharmacology, pharmacokinetics and toxicology of etravirine. The studies were conducted considering European and international guidelines. Pivotal non-clinical studies were conducted in accordance with international GLP guidelines.

Etravirine has been used in 3 forms, initially in base-form and subsequently as the hydrogen bromide (HBr) salt. These forms are referred to as etravirine base and etravirine HBr, respectively. At a later stage of development, a spray-dried form of the base became available which is referred to as spray-dried etravirine. The dose levels used in all studies are expressed as base equivalent.

Several aspects of the nonclinical programme were subject to central scientific advice: (1) the toxicology studies for the qualification of some specified impurities; (2) impurities formed in the manufacture of etravirine; (3) 1-month bridging toxicity study in dogs; (4) the submission of carcinogenicity study reports post-approval. The outcome of the respective advice was addressed in the MAA dossier.

Pharmacology

The mode of action related to the antiviral activity as well as resistance aspects are also discussed in the section "Clinical Aspects, Pharmacodynamics".

- Primary pharmacodynamics

Etravirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor selected for its high antiviral potency against wildtype and non-nucleoside reverse transcriptase inhibitor-resistant HIV-1. The inhibition of enzymatic activity of recombinant wildtype HIV-1 reverse transcriptase by etravirine was characterized by an IC_{50} of 38.40 nM.

Cocrystallization and molecular modelling studies suggested that etravirine is a flexible molecule able to bind in the non-nucleoside reverse transcriptase inhibitor binding pocket of the HIV-1 reverse transcriptase in multiple conformations. The flexibility of etravirine may increase its ability to adapt the binding to HIV-1 reverse transcriptases containing amino acid substitutions associated with resistance to non-nucleoside reverse transcriptase inhibitors, which may explain the resilience of etravirine to non-nucleoside reverse transcriptase inhibitor resistance-associated mutations. *In vitro* studies in human T-cell lines and in human primary cells showed that etravirine inhibited wildtype laboratory and primary HIV-1 isolates of different origins and subtypes, with median EC_{50} values ranging from 0.87 to 5.46 nM. Overall, etravirine showed an antiviral activity profile consistent with the mode of action as a non nucleoside reverse transcriptase inhibitor as measured by time of addition and multiplicity of infection experiments.

In vitro selection experiments were performed to determine the rate of emergence of resistant viruses as well as the mutations associated with decreased susceptibility to etravirine upon selective pressure. Starting from wildtype HIV-1 of different origins and subtypes, experiments performed at high multiplicity of infection, showed that the emergence of resistant strains was delayed or prevented at etravirine concentrations of $\leq$ 200 nM, whereas efavirenz and nevirapine did not prevent virus breakthrough.

Etravirine showed *in vitro* antiviral potency against 56 of 65 HIV-1 mutant strains, each having an amino acid substitution at a position associated with resistance to non-nucleoside reverse transcriptase inhibitors and including the most commonly found K103N and Y181C. Analyses performed on these site-directed mutants showed that there was limited cross-resistance between etravirine and efavirenz. Only 3 of these 65 viruses exhibited a loss in susceptibility for both drugs. Of note, treatment with nevirapine or efavirenz of subjects failing an etravirine containing regimen is not recommended. The

combination of the V179F with either the Y181C or Y181I was associated with the highest etravirine fold change in EC_{50} value. The antiviral activity of etravirine against HIV-1 viral strains with multiple amino acid substitutions at positions associated with resistance to nucleoside reverse transcriptase and/or protease inhibitors was comparable to that observed against wildtype HIV-1.

The antiviral activity of etravirine against non-nucleoside reverse transcriptase inhibitor resistant HIV-1 was assessed using a panel of 6171 HIV-1 non-nucleoside reverse transcriptase inhibitor-resistant recombinant clinical isolates. Etravirine exhibited a higher antiviral activity on a larger proportion of viruses from this panel than the approved nonnucleoside reverse transcriptase inhibitors, having EC_{50} values equal to or below 10 nM for 83.2% of the viruses and EC_{50} values above 100 nM for only 2.0% of the viruses.

- Secondary pharmacodynamics

No inhibitions of the human DNA polymerases alpha, beta, and gamma were observed, indicating the specificity of etravirine for HIV reverse transcriptase. No antiviral activity of etravirine was observed against bovine diarrhea virus, hepatitis B virus, hepatitis C virus, herpes simplex virus 1, herpes simplex virus 2, human coronavirus, influenza virus, moloney murine sarcoma virus, sindbis virus, vaccinia virus, vesicular stomatitis virus, or yellow fever virus.

A series of *in vitro* secondary pharmacodynamic studies was conducted. Etravirine only weakly interacted with glycine-1 transporter binding sites (inhibition constant (Ki) was 5.4 μM). No interaction of the compound with receptors could be observed in any other assays performed. At concentrations of 1 and 10 μM etravirine was found to have inhibitory effects on nicotinergic nerve-smooth muscle function, but was devoid of muscarinic effects.

- Safety pharmacology programme

No relevant treatment-related effects were observed on ECG, cardio-hemodynamic or respiratory parameters in dogs after the administration of oral doses up to 400 mg/kg. No relevant effects on neurobehavioral, motor activity or other body functions were seen in rats following oral administration of up to 80 or 500 mg/kg etravirine base or spray-dried etravirine. Dosing at 500 mg/kg led to a slight delay in righting reflex but behavioural and autonomic functions were unaffected and there were no other relevant effects.

- Pharmacodynamic drug interactions

In vitro combination experiments showed that etravirine was not antagonistic with any of the approved antiretroviral compounds.

Pharmacokinetics

Animal pharmacokinetic studies were conducted in CD1, NMRI and CB6F1-nonTgrasH2-transgenic mice, pigmented Lister-Hooded,Wistar and Sprague-Dawley rats, SPF albino or New Zealand white rabbits and Beagle dogs. With the exception of pigmented rats, all species and strains were the same as those used in the nonclinical pharmacology and toxicology studies.

Analytical methods (LC-MS/MS) have been adequately validated. Analysis of pharmacokinetic and toxicokinetic data from nonclinical studies was performed using non-compartmental methods.

Absorption/Bioavailability

Despite etravirine being classified as a compound with low to intermediate permeability in the *in vitro* Caco-2 model, etravirine was poorly absorbed likely because of low solubility and dissolution rate. Moreover oral absorption was highly variable. Spray dried formulation and food seemed to improve absorption. Following oral gavage administration, peak plasma concentrations were generally reached within 4 hours in all species, and the elimination from plasma was rapid. Across the dose range

studied, plasma levels of etravirine increased less than dose proportionally, especially at the high dose levels, probably due to poor solubility. There were no major gender differences. In all species, the systemic exposure decreased after repeated dosing, especially at doses where high exposure values are achieved in the first day of dosing, likely due to CYP activity induction, as shown in *in vitro* studies.

The recommended clinical dose of etravirine for treatment-experienced HIV-infected patients is 200 mg twice daily (formulation F060). At this dose level, the mean Cmax was 0.451 µg/mL and the mean area under the curve (AUC0-24h) was 7.4 µg.h/mL in HIV-infected patients after 8 days of treatment. After comparison of these values with the highest doses and exposures achieved in animal species after repeated administration, the AUC ratio (animal/human) was 8 in dogs and was around 1 in mice, female Sprague-Dawley rats and rabbits but was less than 1 in male Sprague-Dawley and Wistar rats. In general, the ratio was influenced by the physical form of the active substance and the duration of drug administration due to enzymatic auto-induction, which reduced exposure upon repeated administration.

Distribution

Etravirine was bound between 99.8% and 99.9% to plasma proteins and this was species and concentration independent. Binding was of the same extent to both human albumin and α1-acid glycoprotein. There were some weaknesses in the tissue distribution study in the rat. However it can be concluded that concentrations of radioactivity in all tissues were higher than in blood or plasma. Highest concentration (excluding gastro intestinal tract) were associated with the liver, fat, adrenal, kidney cortex and preputial gland, tissue to plasma concentrations ratios were 27, 11, 10, 8.6, and 6.7, respectively. Lowest concentrations were associated with bone, seminal vesicle and eye, the tissue to plasma concentration ratios were 1.1, 1.0, and 1.5, respectively.

Metabolism/Excretion

The metabolism of etravirine following a single oral administration was quantitatively limited in rodents, dogs and humans. In human liver microsomes (HLM), CYP3A4 enzyme, and to a lesser extent also the CYP2C enzyme, played a major role in the biotransformation of etravirine. Etravirine inhibited CYP2C9 in HLM with an inhibition constant (Ki) value of 0.58 µM (0.25 µg/mL). *Ex vivo* induction studies in rodents showed that etravirine was an inducer of CYP3A and CYP2B isoenzymes and, to a lesser extent, of cytosolic glutathione-*S*-transferase (GST) activity. Etravirine induced uridine diphosphate-glucuronosyltransferase (UDP-GT) activity in mice and to a lesser extent in rats. *Ex vivo* induction studies in dogs showed that etravirine had an inducing effect on CYP3A and possibly also on CYP2B and other CYP subfamily isoenzymes, however, to a much lesser extent than in rodents.

In all animal species dosed with ^{14}C-etravirine, TR was excreted rapidly via the faecal route. At 24 hours after dosing 78% to 87% of TR was eliminated in mice, 84% to 93% in rats and 90% in dogs. At 48 hours after dosing, about 60%, 85% and 82% of the radioactive dose was excreted as unchanged etravirine in the faeces of mice, rats and dogs, respectively. Renal excretion was very limited (0.2% to 0.6% of the radioactive dose) in all animal species and no or only very small amounts (< 0.03% of the radioactive dose) of unchanged etravirine could be detected in urine. The excretion was virtually complete at 96 hours after dosing in rodents and at 168 hours after dosing in dogs. In humans, excretion was almost complete at 168 hours after dosing with 93.7% of the administered dose excreted via the faeces and only 1.2% via the urine. Also in humans, 81.2% to 86.4% of the dose was excreted as unchanged etravirine in the faeces.

In animal and human plasma etravirine accounted for nearly all radioactivity. In all species, as etravirine is poorly absorbed, radioactivity was very low in urine (and bile in rat) and no etravirine was detected. In faeces, radioactivity was abundant, likely due to etravirine which was not absorbed. Total radioactivity balance was complete in all species, including human.

Toxicology

Etravirine was studied in single and repeated dose toxicity studies up to and including 3 months in

mice, 6 months in rats and 12 months in Beagle dogs, a series of genetic toxicity studies and reproductive and developmental toxicity studies covering fertility to postnatal development. In all pivotal repeated dose toxicity studies plasma levels of etravirine have been determined. Several formulations of etravirine were tested: etravirine base, etravirine HBr salt and a spray-dried form corresponding to an amorphous form containing hydroxypropylmethylcellulose. Most of the toxicological studies were performed using etravirine HBr salt. Since the spray-dried form was developed later in the programme, some of the toxicological studies were repeated using this form.

- Single dose toxicity

Acute toxicity studies in mice and rats did not show relevant effects following oral administration of etravirine base or etravirine HBr in PEG 400 vehicle at doses up to 1000 mg/kg. In dogs, a dose-escalation phase up to 160 mg/kg was followed by a 5-day repeated dose phase at 120 mg/kg/day using tablets. In the third phase, dogs were given 350 mg/kg/day of spray-dried etravirine in an aqueous suspension by oral gavage for 5 consecutive days in fasted or fed conditions. No relevant toxicity findings were observed.

- Repeat dose toxicity

In oral repeat-dose in Wistar rats, etravirine base in PEG 400 vehicle was used in a 2-week study but subsequently etravirine HBr formulated in PEG 400 was used in 1-, 3- and 6-month studies. The changes seen in liver and thyroid (cellular hypertrophy with increase in organ weight) were consistent with the liver enzyme inducing property of etravirine and are considered to reflect an adaptive response to liver enzyme induction. The NOAEL in the 6-month study was 70mg/kg/day.

In dogs, etravirine base in PEG 400 vehicle was evaluated by oral (gavage) administration in a 2-week and a 1-month study but subsequently etravirine HBr formulated in PEG 400 was used in 3-, 6- and 12-month studies. The spray-dried form was tested as an aqueous suspension in dogs in 1- and 6-month studies. Repeated dosing with spray-dried etravirine resulted also in liver changes (increases in transaminases, microgranuloma and minor inflammatory changes, and inspissated bile in gall bladder). The NOAEL in the 12-month study was 240 mg/kg/day.

- Genotoxicity

The *in vitro* and *in vivo* genotoxicity tests (Ames, mouse lymphoma, human lymphocytes tests and mouse bone marrow micronucleus) are detailed in Tables 1 and 2. All studies have shown etravirine to be free of genotoxic potential, with and without liver metabolic activation system.

Table 1 *In vitro* genotoxicity studies conducted with etravirine

Assay	Indicator cells	Doses	Results	GLP
Ames Bacterial Reversion (S9mix +/-)	Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537	0 (vehicle), 5, 10, 25, 50, 100, 250, 500 µg/plate (Base)	Negative	**Yes**
	Salmonella typhimurium TA98, TA100, TA1535, TA1537 Escherichia coli WP2uvrA	0 (vehicle), 3, 10, 33, 100, 333 µg/plate (Base)	Negative	**Yes**
Mouse lymphoma cells	L5178Y TK+/-	Up to 100 µg/mL vehicle (Base)	Negative	**Yes**
Mammalian chromosome aberration (S9mix +/-)	Human peripheral Lymphocytes	Up to 100 µg/mL vehicle (Base)	Negative	**Yes**

Table 2 ***In vivo*** **genotoxicity studies conducted with etravirine**

Assay	Indicator cells	Route of administration	Doses (mg/kg)	Results	GLP
Micronucleus	Mouse/ NMRI BR	Oral/Gavage (single dose)	0 (vehicle), 2000 (HBr salt)	Negative	**Yes**

- Carcinogenicity

Long-term carcinogenicity studies are currently being evaluated (dosing completed, histopathology in progress) and the results will be provided by the applicant as post-approval commitment. The lack of the carcinogenicity data was considered acceptable by the CHMP as the medicinal product does address an unmet medical need and is intended for the treatment of patients with limited treatment options.

Dose range finding studies in the mouse and rat have been completed with etravirine HBr, formulated in PEG 400, given by oral gavage, or spray-dried etravirine administered via the diet. The use of transgenic RasH2 mice has been explored in a dose range finding study, but it was decided to conduct a classical 2-year carcinogenicity study in CD1 mice.

In rats, results obtained in these studies were comparable to the one obtained in repeated-toxicity studies. Of note that an increase in PT and APTT was observed in males without concomitant bleeding. In mice, etravirine also induced liver hypertrophy as observed in the rats. However, in mice the effects on the coagulation was much more pronounced compared to rats leading to hemorrhagic cardiomyopathy often associated with hemothorax and haemorrhages in several organs.

- Reproduction Toxicity

No relevant effects on male or female fertility were observed in a study performed with etravirine HBr in PEG 400 up to a dose level of 506 mg/kg/day. No relevant effects were observed in a study with spray-dried etravirine suspended in water and the NOAEL was roughly 500 mg/kg/day. In an embryo-foetal developmental toxicity study pregnant rats were dosed with etravirine HBr in PEG 400 up to 1000 mg/kg/day and this did not result in maternal or foetal toxicity. The foetal NOAEL was 1000 mg/kg/day and etravirine is therefore considered not to be teratogenic in the rat. In an embryo-foetal developmental toxicity study etravirine HBr, formulated in alpha-tocopheryl polyethylene glycol succinate (TPGS)/HPMC, was dosed in pregnant rabbits up to 750 mg/kg/day. Etravirine has shown no teratogenic potential. Therefore, an additional study was conducted using spray-dried etravirine suspended in water and at doses up to 375 mg/kg/day. The maternal NOAEL was 125 mg/kg/day and foetal NOAEL was 375 mg/kg/day. No adverse effects were observed in a pre- and postnatal development study in the rat using spray-dried etravirine at dose levels up to 500 mg/kg/day. The maternal NOAEL was 500 mg/kg/day.

- Toxicokinetic data

At high dose or exposure levels, C_{max} and AUC values decreased after repeated administration due to metabolic auto-induction. At the recommended clinical dose regimen (200 mg twice daily) in treatment experienced HIV-1 infected subjects, the exposure is equivalent to a C_{max} value of 0.45 µg/mL and an $AUC_{0\text{-}24h}$ of 7.4 µg.h/mL. The safety margin for etravirine, expressed on the basis of AUC, is close to or less than 1 in rodents but up to about 5 in dogs at the recommended clinical dose regimen.

- Local tolerance

Etravirine was classified as "nonsensitizing" based on an *in vivo* guinea pig skin sensitization study and was also found to be unlikely to cause skin sensitization in a mouse local lymph node assay (LLNA). Etravirine was also classified as "nonirritant" based on an *in vivo* rabbit skin irritation study. In an *in vitro* eye irritation assay, etravirine base was considered as a "mild" eye irritant, whereas etravirine HBr was considered as a "very severe" eye irritant. No effects were observed in an *in vitro* phototoxicity study.

- Other toxicity studies

Studies in juvenile animals were not conducted. The embryofoetal studies in rats have revealed some skeletal variants which have been attributed to a possible slower development. Since thyroid function may have been affected by etravirine in line to the liver enzyme induction effects, the possibility for a mechanistic explanation for this growth retardation-related effect to be associated to the reduced maternal thyroid function should be considered.

Concerning the immunotoxicity aspects, there were no relevant effects of treatment with etravirine HBr formulated in PEG 400 and the immune response, as measured by IgM production, was not affected by treatment.

The mechanistic studies conducted with etravirine suggested that the effect of etravirine on clotting times and clotting factors in mice is mediated via a vitamin K pathway (Table 3). The underlying mechanism for the cardiac lesions can be explained by the severely disturbed coagulation resulting in interstitial hemorrhagic diathesis within the myocardium and subsequent muscle degeneration and inflammation. The mouse is thought to be more sensitive to develop hemorrhagic cardiomyopathy due to a higher heart rate and thinner ventricular and atrial wall, relative to other species. The exact mechanism of etravirine on the vitamin K pathway is not known. However, results obtained in clinical studies seem to show that etravirine is not affecting the coagulation parameters in patients.

Table 3 Mechanistic studies in mouse with etravirine

Species/Strain No. and Gender/Group	Route of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg base equivalent/kg/day)	Noteworthy Findings
Mouse/CD1 20M + 20F (main) 8M + 8F (satellite)	Oral/dietary admixture (diet)	6 Weeks	0 (untreated diet), 0 (untreated diet + Vitamin K1 sc), 2320, 2320 (+ Vitamin K1 sc) as spray-dried etravirine (1:2:0.5 active to polymer ratio)	- Etravirine alone: 1M showed hemorrhagic cardiomyopathy. No haemorrhages in any other organ. ↑ APTT + PT and ↓ vitamin K dependent factors II and VII. These effects were more pronounced in males. - Etravirine with Vitamin K: normalization of coagulation times and clotting factors II and VII. Reduction of hepatic hemorrhagic necrosis.
Mouse/CD1 20M + 20F (main) 8M + 8F (satellite)	Oral/gavage (PEG 400)	4 Weeks	0 (vehicle), 0 (vehicle + Vitamin K1 sc), 1000, 1000 (+ Vitamin K1 sc) as etravirine HBr	- No animals with hemorrhagic cardiomyopathy. No haemorrhages in any other organ. - Etravirine alone: ↑ APTT + PT and ↓ vitamin K dependent factors II and VII. These effects were more pronounced in males. No effects on factor II and VII in females. - Etravirine with Vitamin K:

			normalization of coagulation times and clotting factors II and VII. Gavage administration of etravirine HBr had lower impact on clotting times compared with dietary admixture.

APTT: activated partial thromboplastin time; F: female; M: male; PEG400: polyethylene glycol 400; PT: prothrombin time; sc: subcutaneous; ↑: increased; ↓: decreased

The impurities R230187 and R405793 were qualified above their specified levels and they were considered non-genotoxic in an Ames test and in a chromosomal aberration test and also non-toxic in a repeated dose (3 months) toxicity study. The impurity R405792 was tested in an Ames test and considered non-mutagenic. Genotoxicity studies (in human lymphocytes or Chinese hamster V79 cells and *in vivo* micronucleus test) conducted on 2 intermediate products, T002615 and T002327 were negative.

Ecotoxicity/environmental risk assessment

An environmental exposure assessment (Phase I) as well as an environmental fate and effect analysis (Phase II) were performed. The environmental assessment of the compound in the terrestrial compartment included studies on aerobic degradation in soil, effects on soil microorganisms, effects on terrestrial plants, acute effects to earthworm and effects on survival and reproduction of Collembola. In soil, the ratio of Predicted PEC/PNEC was below 1 (6.6×10^{-5}). Because etravirine is highly adsorbed on soil (K_{oc} 16.614 L/kg) and not readily biodegradable (DT_{50} in soil 587 days), an additional sediment dweller test is currently being performed; the results from this study will be provided as post-approval commitment. Zebra Fish in an early-life stage toxicity test was performed, and no toxic effects were noted.

2.4 Clinical aspects

Introduction

The main clinical programme to support the present marketing authorisation application comprised the following studies:

- Two identically designed Phase III pivotal studies to support the claimed indication, C206 (DUET-1) and C216 (DUET-2). Both are randomized, double-blind, placebo-controlled studies in treatment-experienced patients with genotypic resistance to currently available NNRTIs with a duration of 48 weeks. The results of the primary analyses performed at 24 weeks are the basis for the present application. An uncontrolled rollover study (C217), where patients receive open-label etravirine, is ongoing.
- Two controlled Phase IIb studies in treatment-experienced patients claimed to support dose selection (C203 and C223).

An overview of the key elements of these studies is provided in Table 4. In addition, several Phase IIa proof-of-principle studies have been conducted, as well as exploratory Phase IIb studies. Finally, an extensive number of Phase I studies provided data on pharmacokinetic properties, drug-drug interaction and safety/tolerability.

The clinical development was consistent with many aspects of the applicable guidelines, and in particular the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02). Several aspects of the clinical programme were subject to central scientific advice, amongst others the investigation of viral resistance, the dose selection for Phase III studies, the overall design of the Phase III studies, the need for a study in renally impaired patients, and details of the drug-drug interaction programme.

With regard to the paediatric development, a dose-finding Phase I study in treatment-experienced HIV-1 infected children and adolescents was ongoing at time of application.

Table 4 Summary of the main clinical studies supporting dose-selection and efficacy evaluation

Protocol	Design / Duration	Treatment	N	Population	Study objectives Combination therapy	Primary Endpoint
Phase IIb						
C203	Randomized, double blinded (during the first 12 weeks), placebo-controlled, 2-stage dose escalating study / 48 weeks with extension to 144 weeks	Etravirine (formulation TF035) 400 mg bid	57	NRTI-, PI-, and NNRTI-experienced HIV-1 infected patients	Doseescalating (combination therapy: individually optimized ART)	Safety (Efficacy not exploitable due to bias in viral load measure-ment)
		Etravirine (formulation TF035) 800 mg bid	74			
		Etravirine (formulation TF035) 1200 mg bid	43			
		placebo	66			
C223	Randomized, active controlled, partially blinded study / 48 weeks	Etravirine (formulation TF035) 400 mg bid	80	HIV-1 infected patients with NNRTI resistance and at least 3 primary PI mutations	Dose finding (combination therapy: at least 2 ARV drugs [NRTIs and/or PIs and/or ENF])	Change in log10 plasma viral load at Week 24
		Etravirine (formulation TF035) 800 mg bid	79			
		Comparator: at least 3 ARV drugs [NRTIs and/or PIs and/or ENF]	40			
Phase III						
C206 DUET-1	Randomized, double-blinded, placebo-controlled study / 48 weeks with extension to 96 weeks	Etravirine (formulation F060) 200 mg bid	304	HIV-1 infected patients with at least 1 NNRTI mutation and with at least 3 primary PI mutations	To show superiority of etravirine (combination therapy: darunavir/ritonavir + OBR)	Proportion of subjects with plasma viral load i.e. < 50 copies / mL at week 24
		placebo	308			
C216 DUET-2		Etravirine (formulation F060) 200 mg bid	295			
		placebo	296			

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

An extensive study programme has been performed to investigate the pharmacokinetics of etravirine. The extent of this programme was particularly due to the development of several pharmaceutical formulations in order to achieve an adequate bioavailability of etravirine, a substance which is characterised by its low solubility and low permeability. Consequently, a significant number of bioequivalence studies between the various intermediate formulations was conducted.

Amongst the various formulations, the following were of particular relevance with regard to the

overall clinical development:

- PEG 4000-based capsule (TF002): early Phase I and Phase IIa studies;
- HPMC tablet using granulo-layering technology (TF035): late Phase I and Phase II studies;
- HPMC tablet using spray-drying technology (F060): pivotal Phase III studies and commercial formulation.

It is noteworthy that despite this extensive programme, the appreciation of the full pharmacokinetic profile of etravirine in the commercial formulation remains difficult, even with the bridge of the bioequivalence studies between the various formulations. Details are outlined below.

Validated LC-MS/MS methods were developed for the determination of etravirine in human heparin plasma, following a liquid-liquid extraction. The range of quantification of the methods was 2.00 to 5000 ng/mL. These analytical methods were fully validated, enabling to produce accurate and precise concentration results of the studied analytes.

Non compartmental analysis was used for the pharmacokinetic analysis, and conventional pharmacokinetic parameters were determined (e.g. C_{max}, t_{max}, AUC, $t_{1/2}$, C_{min}). Population pharmacokinetic analyses were performed using NONMEM; the First Order Conditional Estimation method (FOCE) with the INTERACTION option and Ln transformed data were used throughout model building and finalisation.

- Absorption

Based on *in vitro* experiments, etravirine is thought to be absorbed via a passive transcellular diffusion mechanism. Moreover, etravirine is an inhibitor of P-gp with an apparent IC_{50} value of 24.2 μM.

Etravirine is absorbed slowly, with median peak concentrations occurring at approximately 4.0 hour (2 to 6 hours depending on the formulation) after fasted oral administration. The absolute bioavailability of etravirine has not been determined because of the lack of an intravenous formulation.

The effect of substances altering intra-gastric pH such as ranitidine and omeprazole on etravirine absorption was investigated (study C120). Ranitidine did not modify etravirine exposure whereas omeprazole increased etravirine exposure. The effect observed with omeprazole was likely related to the inhibition of CYP2C19. Therefore, based on the results obtained with ranitidine, it was concluded that gastric pH did not significantly alter etravirine absorption

<u>Bioequivalence</u>

Of the various bioequivalence studies performed, studies C141, C228 and C229 (sub-study) were considered to be most relevant as they investigated one of the exploratory formulations used in several late Phase I and Phase II studies (TF035) and the final commercial formulation used in the Phase III studies (F060). All these studies were conducted in HIV-1 infected patients. Of note, no bioequivalence study was performed between formulation TF002 and either formulation TF035 or formulation F060. However, given that TF002 was used only at an early stage of the development, for exploratory studies, such a bioequivalence study was not considered mandatory.

Based on the available bioequivalence data, 200 mg b.i.d. of etravirine in the commercial formulation is expected to achieve a higher exposure (30 to 70% depending on the study) as compared to 800 mg b.i.d. of etravirine in formulation TF035. Given the supra-bioavailability of etravirine in the commercial formulation compared to this exploratory formulation, the extrapolation of some pharmacokinetic studies will mandate caution. The details of these most relevant bioequivalence studies are described below.

Study C141

This was a randomized, open-label, single-dose cross-over study to evaluate the relative bioavailability of 3 doses of etravirine as a spray-dry formulation (F060) compared to the granulo-layered formulation (TF035) in 36 HIV-1 infected patients. Subjects were randomized in 3 parallel groups:

- Single dose of 100 mg etravirine as formulation F060 (test) or a single dose of 800 mg etravirine as formulation TF035 (reference);
- Single dose of 200 mg etravirine as formulation F060 (test) or a single dose of 1600 mg etravirine as formulation TF035 (reference);
- Single dose of 300 mg etravirine as formulation F060 (test) or a single dose of 2400 mg etravirine as formulation TF035 (reference).

All treatments were taken under fed conditions within 10 minutes after completion of a standardized breakfast. The washout period between treatments was 14 days.

This study confirmed the improved bioavailability of the commercial formulation (F060) compared to the exploratory formulation (TF035), since 100 mg etravirine in formulation F060 gave the same exposure as 800 mg etravirine in formulation TF035. The bioequivalence was no longer achieved when comparing 300 mg of etravirine in formulation F060 with 2400 mg of etravirine in formulation TF035 (AUC_{last} ratio = 2.13). The test formulation F060 showed a more than dose-proportional increase in pharmacokinetic parameters with increasing doses of etravirine. The test formulation TF035 showed a more than proportional increase in exposure between 800 mg and 1600 mg. No additional increase in exposure was observed with the 2400 mg dose.

Study C228

This was a randomized, open-label, multiple-dose cross-over study to evaluate the relative bioavailability of etravirine as the commercial formulation (F060) compared to the exploratory formulation TF035 in HIV-1 infected patients. The trial was originally designed to compare 100 mg etravirine b.i.d. in formulation F060 with 800 mg etravirine b.i.d. in formulation TF035, in each case for 7 days with an additional morning intake on Day 8. The trial medication was taken under fed conditions, within 10 minutes after completion of a standardized breakfast. The original protocol was amended to implement an additional group in which subjects received 200 mg etravirine b.i.d. in formulation F060 for 7 days with an additional morning intake on Day 8.

The pharmacokinetic data obtained are shown in Tables 5 and 6. Contrarily to study C141, these results obtained after multiple-dosing did not confirm the bioequivalence between 100 mg etravirine in F060 and 800 mg etravirine in formulation TF035 when administered as single-dose. Moreover, 100 mg multiple-dose etravirine in formulation F060 gave about half exposure of that obtained with 800 mg multiple-dose etravirine in formulation TF035.

With the 200 mg multiple-dose etravirine in formulation F060, the etravirine exposure was about 70% higher than that obtained with 800 mg multiple-dose etravirine in formulation TF035. A greater than dose proportional increase was observed between the 100 mg b.i.d. and the 200 mg b.i.d. dose for etravirine in formulation F060.

Table 5 Pharmacokinetic data following multiple dose administration of 100 mg etravirine b.i.d. in the commercial formulation F060 or 800 mg etravirine b.i.d. in the exploratory formulation TF035 (study C228)

Pharmacokinetics of etravirine mean ± SD, t_{max} median [range]	100 mg etravirine Test (F060)	800 mg etravirine Reference (TF035)	LSmean ratio (90% CI), % Test/Reference
Day 1			
N	33	32	-
$t_{max,}$ h	4.00 [2.00 – 6.00]	4.00 [2.00 – 8.00]	-
$C_{max,}$ ng/mL	54.9 ± 54.0	70.6 ± 72.7	81 (65 – 100)
$AUC_{12h,}$ ng.h/mL	312 ± 331	434 ± 437	72* (59 – 88)
Day 8			
N	33	32	-
$t_{max,}$ h	4.00 [0.00 – 6.00]	4.00 [0.00 – 6.00]	-
$C_{0h,}$ ng/mL	86.3 ± 84.5	148.8 ± 119.3	-
$C_{min,}$ ng/mL	59.9 ± 63.8	125.8 ± 116.4	47*** (38 – 59)
$C_{max,}$ ng/mL	170.9 ± 99.9	318.8 ± 245.8	61** (50 – 75)
$AUC_{12h,}$ ng.h/mL	1284 ± 958	2607 ± 2135	54*** (44 – 65)
$C_{ss,av,}$ ng/mL	107.0 ± 79.8	217.3 ± 177.9	-
FI, %	125.2 ± 47.7	94.9 ± 35.5	-

LSmean = least square mean; CI = confidence interval; SD = standard deviation
Levels of significance: *p ≤0.05, **p ≤0.01, ***p ≤0.001.

Table 6 Pharmacokinetic data following multiple dose administration of 200 mg etravirine b.i.d. in the commercial formulation F060 or 800 mg etravirine b.i.d. in the exploratory formulation TF035 (study C228)

Pharmacokinetics of etravirine mean ± SD, t_{max} median [range]	200 mg etravirine Test (F060)	800 mg etravirine Reference (TF035)	LSmean ratio (90% CI), % Test/Reference
Day 1			
N	27	32	-
$t_{max,}$ h	4.00 [3.00 – 8.00]	4.00 [2.00 – 8.00]	-
$C_{max,}$ ng/mL	125.9 ± 109.6	70.6 ± 72.7	197*** (159 – 245)
$AUC_{12h,}$ ng.h/mL	745 ± 660	434 ± 437	191*** (154 – 236)
Day 8			
N	27	32	-
$t_{max,}$ h	4.00 [2.00 – 8.00]	4.00 [0.00 – 6.00]	-
$C_{0h,}$ ng/mL	235.9 ± 163.1	148.8 ± 119.3	-
$C_{min,}$ ng/mL	184.7 ± 128.1	125.8 ± 116.4	167** (137 – 204)
$C_{max,}$ ng/mL	451.3 ± 232.3	318.8 ± 245.8	167** (137 – 204)
$AUC_{12h,}$ ng.h/mL	3713 ± 2069	2607 ± 2135	167*** (138 – 202)
$C_{ss,av,}$ ng/mL	309.5 ± 172.4	217.3 ± 177.9	-
FI, %	95.3 ± 31.4	94.9 ± 35.5	-

LSmean = least square mean; CI = confidence interval; SD = standard deviation
Levels of significance: *p ≤0.05, **p ≤0.01, ***p ≤0.001.

Although no bioequivalence was demonstrated with the 100 mg b.i.d. or the 200 mg b.i.d. dosing of etravirine in the commercial formulation compared to the 800 mg b.i.d. dosing of etravirine in the exploratory formulation TF035, the range of exposure to etravirine was comparable between the 200 mg b.i.d. dose of the commercial formulation and the 800 mg b.i.d. dose of formulation TF035 after multiple dosing in HIV-1 infected subjects. Based on these results, the 200 mg b.i.d. dose of etravirine administered as formulation F060 was selected for further clinical development, including the Phase III trials.

Study C229

This is an ongoing Phase IIb, open-label, rollover study in HIV-1 infected subjects to evaluate the long-term efficacy, safety, and tolerability of etravirine administered as part of an individually optimized ART. All subjects received etravirine at a dose of 800 mg b.i.d. in formulation TF035 until the new formulation F060 was available, after which all subjects were switched to etravirine at a dose

of 200 mg b.i.d. (formulation F060). A sub-study to evaluate the pharmacokinetic profile of etravirine at Week 4 of treatment with each formulation was conducted in a subset of subjects, enabling an intra-subject comparison to be made of the pharmacokinetics of etravirine with the earlier formulation TF035 and the new formulation F060.

The pharmacokinetic data obtained are shown in Table 7. In this study, the bioavailability of etravirine was increased by 30% with the commercial formulation (200 mg b.i.d.) compared to the TF035 formulation (800 mg b.i.d.). The range of exposures was comparable with both formulations.

Table 7 Pharmacokinetic data following multiple dose administration of 200 mg etravirine b.i.d. in the commercial formulation F060 or 800 mg etravirine b.i.d. in the exploratory formulation TF035 (sub-study C229)

Parameter	Mean ± SD, $t_{max:}$ Median (Range)		Ratio [a] (Test:Reference)	90% CI
	Etravirine 800 mg b.i.d. TF035 (Reference)	Etravirine 200 mg b.i.d. F060 (Test)		
N	15	15		
$t_{max,}$ h	4.00 (2.00 – 9.00)	3.00 (0.00 – 6.00)	-	-
$C_{0h,}$ ng/mL	346.3 ± 278.5	557.0 ± 421.9	-	-
$C_{min,}$ ng/mL	309.7 ± 256.8	418.2 ± 325.2	1.32	1.00 – 1.74
$C_{max,}$ ng/mL	629.0 ± 426.4	805.6 ± 524.2	1.32	1.04 – 1.68
$C_{ss,av,}$ ng/mL	469.3 ± 336.3	594.8 ± 418.5	-	-
$AUC_{12h,}$ ng.h/mL	5513 ± 3844	7115 ± 5018	1.28	1.00 – 1.64
FI, %	78.59 ± 35.15	82.77 ± 45.70	-	-

N = maximum number of subjects with data.
[a] Ratio based on LS means

Since the results of this study in terms of increase in exposure between the commercial formulation and the exploratory formulation TF035 differ from the ones obtained in study C228 (30% and 70%, respectively), this aspect was specifically discussed during the MAA assessment. An attempt was made to explain this difference by correlation with the exposure observed in individual patients. Overall this difference was however not considered critical.

Food effect

The food effect on the bioavailability of etravirine, administered as the commercial formulation, has been investigated in two Phase I studies (C147 and C116) performed in healthy subjects. In addition, several studies have been performed to assess the food influence on etravirine absorption using other exploratory formulations of etravirine. All these studies demonstrated consistently that etravirine should be taken after a meal to increase its bioavailability (up to 50%). Accordingly, the SmPC recommends etravirine to be taken following a meal.

- Distribution

Etravirine is extensively bound to plasma protein (99%). Etravirine is essentially bound to human albumin (99.60% at a physiological concentration of 4.3%) and to α1-acid glycoprotein (97.66% to 99.02% at physiological concentrations of 0.10% to 0.20%). The etravirine blood to plasma concentration ratio determined in man was approximately 0.7, indicating no accumulation in the red blood cells.

A limitation of the data is that the distribution of etravirine into compartments other than plasma, like cerebrospinal fluid or genital tract secretions, has not been studied in humans.

- Elimination

Metabolism

The most important Phase 1 metabolic pathway of etravirine in humans was hydroxylation followed by a glucuronidation. Roughly only ca. 11 % of administered etravirine is metabolised. *In vitro*, etravirine was shown to be mainly metabolized by CYP3A and CYP2C (see section "Non-clinical aspects").

A cocktail study was performed in healthy subjects using the commercial formulation (study C174). It was shown that etravirine had no effect on the activity of CYP1A2 and CYP2D6. Moreover, etravirine was shown to be a substrate and a weak inducer of CYP3A4, as well as a substrate and a weak inhibitor of CYP2C9 and CYP2C19.

Excretion

A clinical mass balance study, which investigated a single 800 mg dose of etravirine in an exploratory formulation (TF002) in male healthy volunteers, showed that 93.7% of the radioactivity was recovered in the faeces whereas only 1.2% was recovered in urine. 168 hours after administration 94.9% of the dose was recovered (mean, based on radioactivity). Unchanged etravirine accounted for the majority of the radioactivity in the faeces (about 80% of the administered dose); no unchanged etravirine was recovered in urine.

The very high percent of etravirine recovered in faeces is likely related to the presence of an entero-hepatic cycle or to a very low bioavailability of the compound. Consequently, the high percentage of etravirine recovered in the faeces is likely to reflect the poor bioavailability of etravirine.

The terminal half-life elimination of etravirine is high (ca. 40 h) likely due to the high binding to plasma proteins.

- Dose proportionality and time dependencies

The available clinical data following single and multiple administration of etravirine in healthy volunteers has limitations to allow for reliable conclusions with regard to dose proportionality of the commercial formulation since these studies have been performed with exploratory formulations. Based on these data the rate of absorption and the time to reach steady-state concentrations (about 7 days) did not appear to be influenced by the dose level or the formulation of etravirine administered. The elimination half-life value was about 60 hours.

Moreover, it is also difficult to fully appreciate dose proportionality from the pharmacokinetic studies performed in HIV-1 infected patients. A particular shortcoming of the data is that the dose-proportionality of etravirine with increasing doses was not investigated in HIV-1 infected patients using the commercial formulation. Pharmacokinetic data with this formulation are only available from a sub-analysis in the phase III studies, however the small sample size of less than 20 patients in each group makes it difficult to draw reliable conclusion.

The CHMP did consider these limitations as unfortunate due to the resulting difficulties in understanding the pharmacokinetic profile of the compound given the multiple changes of the formulation. Therefore, the applicant was requested to further discuss the dose and time-dependency of the pharmacokinetics of etravirine in HIV infected patients. In conclusion, it seems that the pharmacokinetics of etravirine appear to be more than dose proportional. The pharmacokinetics after b.i.d. administration has not been investigated at doses exceeding 200 mg b.i.d. in the commercial formulation.

No time-dependent pharmacokinetics was observed in either the pharmacokinetic sub-studies of DUET or in the main DUET trials using population pharmacokinetics over 24 weeks.

- Intra- and inter-individual variability

Based on the PK population, etravirine appears to exhibit a large inter- (approximately 80%) and intra-individual (approximately 40%) variability in pharmacokinetic parameters.

- Pharmacokinetics in target population

Overall the etravirine exposure appears to be lower in HIV-1 infected patients than in healthy subjects (35 to 50%). This difference might be related to a difference in absorption. This information is included in the SmPC.

- Special populations

Renal impairment

Since the renal elimination of etravirine is negligible, the pharmacokinetics have not specifically been explored in subjects with renal impairment. The lack of a clinical study with patients presenting renal impairment was considered acceptable by the CHMP.

Hepatic impairment

In patients with mild or moderate hepatic impairment the pharmacokinetic parameters C_{min} and AUC are slightly decreased (18% or less) compared to control subjects. However, the variability of pharmacokinetic parameters is increased in patients with hepatic impairment compared to control subjects. No dose adjustment is recommended for etravirine in subjects with mild or moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) were not included in the clinical studies. The SmPC in section 4.2 contains a precautionary statement that etravirine is not recommended in patients with severe hepatic impairment.

Others

Due to the homogeneity of population enrolled in clinical studies, few data are available in elderly or from races different from the Caucasian one. A difference in treatment response was observed in Latin America and USA/Canada compared to the EU (trend for lower response in the EU population) that will need to be further explored with the additional confirmatory study that is subject to the post-approval commitments.

The population PK analysis has identified body weight and HBV/HCV-co-infection as factors altering the pharmacokinetics of etravirine. Lower body-weight as well as hepatitis B and/or C co-infection appeared to increase etravirine exposure. It is noteworthy that a decrease in etravirine clearance by 24% was observed in HCV co-infected patients compared to not HCV-infected subject; this aspect will need to be further explored in ongoing and planned studies (e.g. the additional confirmatory study).

The SmPC in section 5.2 adequately describes the current knowledge, particularly the decreased clearance in co-infected patients potentially leading to an increased exposure and altered safety profile of etravirine.

A paediatric development of etravirine is currently ongoing and the applicant committed to provide study reports post-approval.

- Pharmacokinetic interaction studies

An extensive study programme has been conducted to investigate the drug-drug interaction profile of etravirine. Most of the studies that provided information for the use of the medicinal product in clinical practice were conducted using either the commercial formulation (F060) or the exploratory formulation TF035. The rationale for extrapolating the interaction data obtained with formulation

TF035 to the commercial tablet formulation was discussed. A few studies from early development stages were performed with the capsule formulation TF002.

Mechanistic study

A cocktail study was performed to evaluate the potential inhibitory/inducing effects of etravirine on the single dose pharmacokinetic of various CYP substrates. It was designed as open-label, 1-way, 2-period, cross-over study using 200 mg etravirine b.i.d. in steady state, administered in the commercial formulation. The compounds of the cocktail were midazolam 0.025 mg/kg intravenously (CYP3A4), dextromethorphan 30 mg orally (CYP2D6), caffeine 150 mg orally (CYP1A2), omeprazole 40 mg orally (CYP2C19), and warfarin 10 mg orally (CYP2C9).

The results confirmed that etravirine is a CYP3A4 inducer (steady-state). Moreover, it is a CYP2C9 (steady-state) and a CYP2C19 (single dose and steady-state) inhibitor. These data are in line with the non-clinical data.

Co-administration with antiretroviral compounds

The design and the results of the interaction studies investigating the co-administration of etravirine with other antiretroviral compounds are summarized in Table 8.

Table 8 Pharmacokinetic data from interaction studies investigating the co-administration of etravirine with other antiretroviral compounds

	Dose/Schedule		**Mean Ratio (90% CI) of etravirine PK Parameters with/without Co-Adm. Drug No Effect = 1**			**Mean Ratio (90% CI) of Co-Administered Drug PK Parameters with/without Co-Adm. Drug No Effect = 1**		
Co-Adm. Drug (Trial)	**Co-Adm. Drug**	**Etravirine**	**Cmax**	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**
Co-Administration with Nucleoside Reverse Transcriptase Inhibitors								
Didanosine (C157)	400 mg q.d. 16 days	800 mg b.i.d. 8 days (TF035)	1.16 (1.02-1.32)	1.11 (0.99-1.25)	1.05 (0.93-1.18)	0.91 (0.58-1.42)	0.99 (0.79-1.25)	-
Tenofovir disoproxil fumarate (C138)	300 mg q.d. 16 days	800 mg b.i.d. 8 days (TF035)	0.70 (0.60-0.82)	0.69 (0.61-0.79)	0.72 (0.65-0.81)	1.15 (1.04-1.29)	1.16 (1.09-1.23)	1.42 (1.11-1.80)
Tenofovir disoproxil fumarate (C177)	300 mg q.d. 16 days	200 mg b.i.d. 8 days (F060)	0.81 (0.75-0.88)	0.81 (0.75-0.88)	0.82 (0.73-0.91)	1.15 (1.04-1.27)	1.15 (1.09-1.21)	1.19 (1.13-1.26)
Co-Administration with Protease Inhibitors								
Unboosted Protease Inhibitors								
Ritonavir (C105)	300 mg b.i.d. 1 day 400 mg b.i.d. 1 day 500 mg b.i.d. 1 day 600 mg b.i.d. 5 days	400 mg single dose (Day 4) (TF002)	0.68 (0.55-0.85)	0.54 (0.41-0.73)	-	NA	NA	NA
Ritonavir (C116)	100 mg single dose	200 mg single dose (F060)	1.00 (0.89-1.12)	1.03 (0.91-1.17)	-	NA	NA	NA
Saquinavir (C106)	1200 mg single dose (Day 14)	900 mg b.i.d. 14 days (TF002)	0.96 (0.88-1.04)	0.98 (0.90-1.06)	-	0.54 (0.34-0.86)	0.48 (0.29-0.80)	-
Indinavir (C111)	800 mg t.i.d. 6 days	1600 mg b.i.d. 14 days	1.51 (1.16-1.97)	1.51 (1.20-1.90)	1.52 (1.20-1.91)	0.72 (0.58-0.89)	0.54 (0.46-0.62)	0.24 (0.17-0.34)

	Dose/Schedule		Mean Ratio (90% CI) of etravirine PK Parameters with/without Co-Adm. Drug No Effect = 1			Mean Ratio (90% CI) of Co-Administered Drug PK Parameters with/without Co-Adm. Drug No Effect = 1		
Co-Adm. Drug (Trial)	**Co-Adm. Drug**	**Etravirine**	**Cmax**	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**
		(TF035)						
Atazanavir (C151)	400 mg q.d. 7 days	800 mg b.i.d. 14 days (TF035)	1.47 (1.36-1.59)	1.50 (1.41-1.59)	1.58 (1.46-1.70)	0.97 (0.73-1.29)	0.83 (0.63-1.09)	0.53 (0.38-0.73)
Boosted Protease Inhibitors								
Atazanavir/ Ritonavir (C151)	300/100 mg qd 7 days	800 mg b.i.d. 14 days (TF035)	1.30 (1.17-1.44)	1.30 (1.18-1.44)	1.26 (1.12-1.42)	0.97 (0.89-1.05)	0.86 (0.79-0.93)	0.62 (0.55-0.71)
Darunavir/ Ritonavir (C139)	600/100 mg b.i.d. 8 days	800 mg b.i.d. 16 days (TF035)	0.66 (0.52-0.84)	0.67 (0.52-0.86)	0.56 (0.40-0.78)	1.26 (1.17-1.35)	1.23 (1.16-1.31)	1.13 (1.05-1.23)
Darunavir/ Ritonavir (C176)	600/100 mg b.i.d. 8 days	100 mg b.i.d. 8 days (F060)	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)	1.03 (0.98-1.09)	1.06 (1.00-1.13)	1.02 (0.89-1.17)
Darunavir/ Ritonavir (C176)	600/100 mg b.i.d. 8 days	200 mg b.i.d. 8 days (F060)	1.81 [a] (1.56-2.11)	1.80 [a] (1.56-2.08)	1.67 [a] (1.38-2.03)	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
Lopinavir/ Ritonavir (C122)	400/100 mg b.i.d. 14 days	1600 mg b.i.d. 21 days (TF035)	1.15 (0.94-1.41)	1.17 (0.96-1.43)	1.23 (0.98-1.53)	0.85 (0.62-1.05)	0.80 (0.49-1.07)	0.92 (0.15-1.68)
Saquinavir/ Ritonavir (C123)	1000/100 mg b.i.d. 14 days	1600 mg b.i.d. 21 days (TF035)	0.63 (0.53-0.75)	0.67 (0.56-0.80)	0.71 (0.58-0.87)	1.00 (0.70-1.42)	0.95 (0.64-1.42)	0.80 (0.46-1.38)
Tipranavir/ Ritonavir (C161)	500/200 mg b.i.d. 16 days	800 mg b.i.d. 16 days (TF035)	0.29 (0.22-0.40)	0.24 (0.18-0.33)	0.18 (0.13-0.25)	1.14 (1.02-1.27)	1.18 (1.03-1.36)	1.24 (0.96-1.59)
Fosamprenavir/ Ritonavir (C117)	700/100 mg b.i.d. ongoing regimen	800 mg b.i.d. 14 days (TF035)	NA	NA	NA	1.62 (1.47-1.79)	1.69 (1.53-1.86)	1.77 (1.39-2.25)
Lopinavir/ Saquinavir/ Ritonavir (C145)	400 mg. b.i.d./ 800-1000 mg. b.i.d./ 100 mg. b.i.d., 14 days	800 mg b.i.d. 14 days (TF035)	NA	NA	NA	0.84 (0.74-0.95) 0.85 (0.61-1.19) 0.89 (0.69-1.15)	0.82 (0.70-0.96) 0.87 (0.62-1.21) 0.87 (0.69-1.12)	0.76 (0.54-1.08) 0.87 (0.60-1.28) 0.88 (0.57-1.37)
Co-Administration with Other Non-Nucleoside Reverse Transcriptase Inhibitors								
Efavirenz (C109)	600 mg q.d. 18 days	900 mg single dose (Day 14) (TF002)	0.83 (0.73-0.93)	0.59 (0.52-0.68)	-	NA	NA	NA
Nevirapine (C109)	200 mg q.d. 7 days followed by 200 mg b.i.d. 11 days	900 mg single dose (Day 14) (TF002)	0.64 [d]	0.45 [d]	-	NA	NA	NA
Co-Administration with Fusion Inhibitors								
Enfuvirtide (DUET-1 [C206] and DUET-2 [C216])	90 mg b.i.d.	200 mg b.i.d. (F060)	-	⇔[c]	⇔[c]	NA	NA	NA
Co-Administration with Integrase Strand Transfer Inhibitors								
Raltegravir (C179)	400 mg b.i.d. 4 days	200 mg b.i.d. 12 days (F060)	1.04 (0.97-1.12)	1.10 (1.03-1.16)	1.17 (1.10-1.26)	0.89 (0.68-1.15)	0.90 (0.68-1.18)	0.66 (0.34-1.26)
Co-Administration with CCR5 Inhibitors								

	Dose/Schedule		Mean Ratio (90% CI) of etravirine PK Parameters with/without Co-Adm. Drug No Effect = 1			Mean Ratio (90% CI) of Co-Administered Drug PK Parameters with/without Co-Adm. Drug No Effect = 1		
Co-Adm. Drug (Trial)	**Co-Adm. Drug**	**Etravirine**	**Cmax**	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**
Maraviroc (C181)	300 mg b.i.d. 10 days	200 mg b.i.d. 10 days (F060)	1.05 (0.95-1.17)	1.06 (0.99-1.14)	1.08 (0.98-1.19)	0.40 (0.28-0.57)	0.47 (0.38-0.58)	0.61 (0.53-0.71)
	150 mg b.i.d. 10 days	200 mg b.i.d. 10 days (F060) plus DRV 600 mg b.i.d. plus RTV 100 mg b.i.d.	NA	NA	NA	1.77[b] (1.20-2.60)	3.10[b] (2.57-3.74)	5.27[b] (4.51-6.15)

NA = not applicable; - = no information available; a In comparison to etravirine 100 mg b.i.d. (formulation F060) for 8 days; b Compared to maraviroc 150 mg b.i.d.; c Based on population pharmacokinetic analysis; d No formal statistical analysis was performed due to small sample size.

The following conclusion can be drawn:

- The interaction studies performed with unboosted protease inhibitors are judged not relevant given that most protease inhibitors are currently used in the EU as boosted with ritonavir.
- Etravirine can be associated with ritonavir-boosted protease inhibitors with the exception of tipranavir/ritonavir which induced a sharp decrease of etravirine exposure (80%). Although unfortunate, since both drugs are intended for salvage therapy, the CHMP acknowledged that a two-way interaction is difficult to overcome for this combination and that the investigation of a dose-adjustment for tipranavir/ritonavir and etravirine appears very difficult. In view of the sharp decrease in etravirine exposure, the SmPC in sections 4.4 and 4.5 discourages such co-administration.
- The co-administration of etravirine with other NNRTIs is not recommended. However, this co-administration is not relevant in clinical practice.
- An unexpected but limited interaction occurred with tenofovir (increase in tenofovir pharmacokinetics; decrease in etravirine pharmacokinetics). This interaction can be considered as not clinically meaningful; as observed with other ARV compounds the mechanism of interaction with tenofovir remains unclear.
- No interaction study has been performed with NRTIs other than didanosine. However, given that the renal elimination of etravirine is expected to be very limited no significant interaction is expected with NRTIs. As regards the co-administration with NRTIs known to be metabolized by glucuronidation (abacavir, zidovudin), a common pathway for etravirine, based on a drug-drug interaction with the uridine diphosphate glucuronosyl transferase substrate raltegravir, no effect on uridine diphosphate glucuronosyl transferase and therefore no clinically relevant effect on glucuronidation is expected.
- The interaction with maraviroc needs to be considered in clinical practice especially given that etravirine will be used in combination with boosted protease inhibitors already known as increasing the maraviroc exposure.

Co-administration with other compounds

The design and the results of the interaction studies investigating the co-administration of ertravirine with other compounds (except ARVs) are summarized in Table 9.

Table 9 Pharmacokinetic data from interaction studies investigating the co-administration of etravirine with other compounds (except ARVs)

	Dose/Schedule		Mean Ratio (90% CI) of etravirine PK Parameters with/without Co-Adm. Drug No Effect = 1			Mean Ratio (90% CI) of Co-Administered Drug PK Parameters with/without Co-Adm. Drug No Effect = 1		
Co-Adm. Drug (Trial)	**Co-Adm. Drug**	**Etravirine**	**Cmax**	**AUC**	**Cmin**	**Cmax**	**AUC**	**Cmin**
Co-Administration with Drugs other than Antiretrovirals								
Atorvastatin (C164) 2-hydroxy atorvastatin	40 mg q.d. 4 days	800 mg b.i.d. 13 days (TF035)	0.97 (0.93-1.02)	1.02 (0.97-1.07)	1.10 (1.02-1.19)	1.04 (0.84-1.30) 1.76 (1.60-1.94)	0.63 (0.58-0.68) 1.27 (1.19-1.36)	- -
Ethinylestradiol/ Norethindrone (C166)	35 µg q.d./ 1 mg q.d., 21 days	200 mg b.i.d. 15 days (F060)	NA	NA	NA	1.33 (1.21-1.46)/ 1.05 (0.98-1.12)	1.22 (1.13-1.31)/ 0.95 (0.90-0.99)	1.09 (1.01-1.18)/ 0.78 (0.68-0.90)
Rifabutin (C156) 25-o-desacetyl rifabutin	300 mg q.d. 14 days	800 mg b.i.d. 21 days (TF035)	0.63 (0.53-0.74)	0.63 (0.54-0.74)	0.65 (0.56-0.74)	0.90 (0.78-1.03) 0.85 (0.75-1.00)	0.83 (0.75-0.94) 0.83 (0.74-0.92)	0.76 (0.66-0.87) 0.78 (0.70-0.87
Sildenafil (C159) *N*-desmethyl sildenafil	50 mg single dose (Day 14)	800 mg b.i.d. 14 days (TF035)	NA	NA	NA	0.55 (0.40-0.75) 0.75 (0.59-0.96)	0.43 (0.36-0.51) 0.59 (0.52-0.68)	- -
Clarithromycin (C171) 14-hydroxy clarithromycin	500 mg b.i.d. 13 days	200 mg b.i.d. 8 days (F060)	1.46 (1.38-1.56)	1.42 (1.34-1.50)	1.46 (1.36-1.58)	0.66 (0.57-0.77) 1.33 (1.13-1.56)	0.61 (0.53-0.69) 1.21 (1.05-1.39)	0.47 (0.38-0.57) 1.05 (0.90-1.22)
Paroxetine (C165)	20 mg q.d. 7 days	800 mg b.i.d. 14 days (TF035)	1.05 (0.96-1.15)	1.01 (0.93-1.10)	1.07 (0.98-1.17)	1.06 (0.95-1.20)	1.03 (0.90-1.18)	0.87 (0.75-1.02)
Omeprazole (C120)	40 mg q.d. 11 days	100 mg single dose (Day 8) (F060)	1.17 (0.96-1.43)	1.41 (1.22-1.62)	-	NA	NA	NA
Ranitidine (C120)	150 mg b.i.d. 11 days	100 mg single dose (Day 8) (F060)	0.94 (0.75-1.17)	0.86 (0.76-0.97)	-	NA	NA	NA
R(-) Methadone (C158) S(+) Methadone	Individual dose regimen ranging from 60 to 130 mg/day	100 mg b.i.d. 14 days (F060)	NA	NA	NA	1.02 (0.96-1.09) 0.89 (0.83-0.97)	1.06 (0.99-1.13) 0.89 (0.82-0.96)	1.10 (1.02-1.19) 0.89 (0.81-0.98)
Digoxin (C180)	0.5 mg single dose (Day 8)	200 mg b.i.d. 12 days (F060)	NA	NA	NA	1.19 (0.96-1.49)	1.18 (0.90-1.56)	-

NA = not applicable; - = no information available.

Etravirine decreased plasma concentrations of drugs metabolized by CYP3A4 and could consequently lead to a loss of efficacy of concerned compounds in particular statins, sildenafil and clarithromycin. Results showed that etravirine can be co-administered with methadone. Some data is available for rifabutin, however the need for further data will need to be discussed as a post-approval commitment. No interaction study with rifampicin has been performed.

Overall, about half of the interaction studies have been performed with the TF035 formulation. Given that 200 mg BID of the commercial formulation will lead to an increased exposure as compared to the

800 mg in the exploratory formulation TF035, results derived from studies with the TF035 formulation might not always describe the "worst case scenario" of the potential interaction.

The SmPC in section 4.5 adequately describes the available pharmacokinetic interaction data. Additional precautionary statements are included as appropriate.

As part of the post-approval commitments, the applicant is requested to provide additional drug-drug interaction data from studies investigating the co-administration of etravirine with lopinavir/ritonavir tablets (in healthy volunteers) and voriconazole, respectively. Furthermore, specific analysis of interaction data is requested from the additional confirmatory study (see below) to substantiate the findings for boosted lopinavir and boosted atazanavir in HIV-infected patients.

- Pharmacokinetics using human biomaterials

In vitro, etravirine was shown to be mainly metabolized by CYP3A and CYP2C. Moreover, etravirine was shown to be a substrate and a weak inducer of CYP3A4, as well as a substrate and a weak inhibitor of CYP2C9 and CYP2C19. Moreover, etravirine is a weak inhibitor of P-gp.

Pharmacodynamics

- Mechanism of action

Etravirine is a non-nucleoside inhibitor of the HIV-1 reverse transcriptase, i.e. it belongs to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs). The HIV-1 reverse transcriptase (RT) produces the proviral DNA, which further integrates into the host cell genome. Etravirine binds directly to the reverse transcriptase and blocks the DNA polymerase activities of reverse transcriptase by causing disruption of the enzyme's catalytic site. No inhibition of the human polymerases alpha, beta and gamma was observed, indicating the specificity of etravirine for the HIV reverse transcriptase.

Details on the pharmacodynamic studies are presented in the section "Non-clinical aspects".

- Primary and Secondary pharmacology

Antiviral activity *in vitro*

Several *in vitro* studies have been performed to characterize the mechanism of action of etravirine. The salient findings are:

- The etravirine EC_{50} values were in the nanomolar range for Wild Type HIV-1 strains and in the micromolar range for Wild Type HIV-2 strains. On Wild Type HIV-1, the antiviral activity is in between nevirapine and efavirenz, much better than nevirapine but slightly lower than efavirenz. However, it is of note that the compound is currently not developed for use in antiretroviral naïve patients.
- Etravirine was shown to inhibit replication of CCR5, CXCR4 and dual-tropic strains of wild type HIV-1 in different host-cells.
- Etravirine was shown to have an antiviral activity against HIV-1 from group M and group O, with EC_{50} values in the nanomolar range for group M isolates and higher values (about 20 nM) for the group O isolates.
- The EC_{50} of etravirine was increased (about 6 fold) in the presence of 50% human serum.

In vitro resistance

Selection experiments were performed in the presence of etravirine to characterize the rate of emergence of resistant viruses and the mutations associated with decreased susceptibility to etravirine upon drug selective pressure. It was shown that:

- Emergence of resistance for wild-type or mutant strains was delayed in the presence of etravirine compared to efavirenz or nevirapine.
- Emergence of resistance needed the selection of multiple mutations.
- The most frequently RT mutations emerging with etravirine were
    - L100I, E138K, V179I, Y181C, and M230I from Wild Type HIV-1;
    - L100I, E138G, V179I, and Y181C from Mutant HIV-1.

The delay in the emergence of mutation and the need for several mutations before the resistance is observed, suggests an improved genetic barrier as compared to existing NNRTIs.

Phenotypic analyses with determination of EC_{50} and FC (fold change in EC_{50}) values on clinical isolates harbouring a loss of susceptibility to at least 1 NNRTI showed that:
- The EC_{50} and FC values were much lower for etravirine compared to delavirdine, nevirapine and efavirenz, in line with a more potent antiretroviral activity of etravirine.
- The percent of isolates for which EC_{50} was $\leq$ 10 nM was much higher for etravirine than for other NNRTIs. Therefore, etravirine showed a wider spectrum of antiretroviral activity than the other NNRTIs.
- The activity of etravirine was consistently higher than that of other NNRTIs, even in isolates harbouring NNRTI RAMs.

The antiretroviral activity of etravirine was assessed (by the measure of the FC value) against mutants harbouring single (n=65), double (n=40) and triple (n=21) NNRTI RAMs introduced by site-directed mutagenesis. A decrease in phenotypic sensibility was exhibited by:
- 9/65 strains harbouring single RAM (Y181C/I/V/T, E138G/Q, K101A/P/Q)
- 22/40 strains harbouring double RAM (V179F + Y181C was associated with the highest increase in FC)
- 15/21 strains harbouring triple RAM with a mutation profile frequently associating L100I, Y181C and K103N. These 15 strains exhibited cross-resistance to efavirenz.

No decreased susceptibility to etravirine was found in viruses harbouring all major NRTI or PI RAMs.

The measure of *in vitro* antiviral activity showed no evidence of antagonism between etravirine and any of the HIV-1 antiretroviral compounds tested.

In vivo resistance

Overall, in the subjects experiencing virologic failure to the etravirine containing regimen, the most frequently emerging NNRTI RAMs were: L100I, K103N, V179F, V179I, Y181C and Y181I. V179F was only observed in combination with Y181C.

Less frequently emerging NNRTI RAMs were A98G, K101P, V108I, I135T, E138G, E138K, E138G, Y181F, Y181G, Y181S, Y181V, H221Y, L228H and M230L.

Most of these mutations matched those identified *in vitro* i.e., L100I, E138K, E138G, V179I, Y181C, and M230I.

A univariate analysis was performed to identify baseline phenotypic and genotypic determinants of decreased virologic response to etravirine at Week 24, in the DUET-1 and DUET-2 trials. These analyses were done in the subgroup of subjects not using *de novo* enfuvirtide, and excluding the subjects who discontinued for other reasons than virologic failure:

- Thirteen mutations were found at baseline to be associated with decreased virologic response to etravirine: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S. These etravirine RAMs have been previously described as NNRTI-RAMs, with the exception of V090I and V106I.

It was shown that the number of these mutations present at baseline was predictive of the virologic response and that the virologic response was lower when at least 3 of these mutations were present.

- The etravirine FC values increased with increasing numbers of etravirine RAMs and were a strong predictor of virologic response. However, based on the available data, a clear breakpoint for FC for etravirine was not established. While the clinical breakpoints might be 3 and 13, this will have to be further substantiated in ongoing/planned studies (including in particular the additional confirmatory study).

Overall, the extensive virologic analysis of *in vitro* and clinical data demonstrated that:

- the resistance profile of etravirine is different from that of other NNRTIs (i.e. efavirenz and nevirapine), with a higher genetic barrier. More than a single mutation is necessary to give rise to resistance and the presence of the mutation K103N alone demonstrated no impact on efficacy. However, as part of the post-approval commitments, the applicant will further explore the influence of the K103N when associated with other etravirine RAMs.
- a list of 13 mutations has been identified (V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S). The virologic response to etravirine has been shown to significantly decrease in the presence of at least 3 of these 13 mutations at baseline.

Although improved as compared to existing NNRTIs, it remains that the genetic barrier of etravirine is limited. Etravirine will have to be adequately "protected" with active components within adequate combination therapy regimens.

Cardiovascular safety studies

In two clinical Phase I trials, a thorough QTc trial (C178) and a Holter monitoring substudy (C153), the effect of etravirine on heart rate and rhythm was evaluated in healthy subjects:

- The thorough QT/QTc trial was a double-blind, double-dummy Phase I trial specifically designed to evaluate the effect of etravirine on the QT/QTc interval. Healthy subjects received 4 different 8-day treatments: 200 mg etravirine b.i.d., 400 mg etravirine q.d., 400 mg moxifloxacin q.d. (included as positive control), and placebo. Etravirine formulation F060 was used. The data of this trial demonstrated that etravirine does not prolong the QT/QTc interval and does not affect other ECG parameters in healthy subjects at clinically relevant doses,
- The Holter monitoring substudy evaluated the effect of 8-day once daily dosing of 400, 800, and 1600 mg etravirine (formulation TF035) on the cardiac rhythm. Rhythm interpretation by the cardiologist revealed no clinically relevant treatment-emergent abnormalities.

- PK/PD relationship

No PK/PD relationship was shown based on the available data. Some statistical analyses suggested that etravirine AUC_{12h} or C_{0h} was a significant predictor of virologic response, but these parameters were less predictive than other covariates tested like baseline viral load or enfuvirtide use. Moreover, no PK/safety relationship has been observed. Therefore it seems not relevant to at this stage to recommend a therapeutic drug monitoring to follow etravirine efficacy or safety. Further data will be needed, like the exploration of the relationship between the PK of etravirine and the primary efficacy endpoint at week 48 in the DUET studies.

Clinical efficacy

Several Phase II studies and two Phase III studies have been performed during the clinical development. These include the following:

- three Phase IIa proof-of-principle studies in treatment-naïve patients (C201 and C208) and in

treatment-experienced patients (C207);
- three Phase IIb studies (C203, C209 and C223) in treatment-experienced patients;
- one exploratory Phase II study (C227) in PI-naïve, NNRTI-experienced patients;
- two roll-over studies derived from patients enrolled in Phase IIb studies (C211 and C229 for patients who were in the control arms and in the etravirine arms, respectively);
- two Phase III studies (C206 or DUET-1, and C216 or DUET-2) in treatment-experienced patients with evidence of NNRTI resistance.

The key elements of the studies most relevant for the present application are summarised in Table 4. For the pivotal Phase III studies, data are available for the whole population at 24 weeks; these studies are ongoing and further data will be provided post-approval. With regard to the Phase II programme it is of note that although the number of studies is high, the overall data set has significant limitations as outlined below for the studies relevant for the dose finding.

- Dose response studies

The choice of the dose investigated in the Phase III studies was based on the following considerations:
- Based on the results of studies C203 and C223, which were both performed using the exploratory formulation TF035, the 800 mg b.i.d. dose was selected for further clinical studies.
- Based on the bioequivalence studies (see section "Clinical aspects, Pharmacokinetics"), 800 mg b.i.d. with formulation TF035 was considered comparable (or inferior) to 200 mg b.i.d. with the commercial formulation.

Given the limitations of the Phase II studies as described below, the dose selection was not considered convincingly substantiated. It was noted though that the supra-bioavailability of the commercial formulation as compared to the TF035 formulation does suggest a potential for improved dose response. Ultimately, the adequacy of the dose can only be appreciated with the results of the Phase III clinical studies.

Study C203

Study 203 was a randomized, double-blind (during the first 12 weeks), placebo-controlled, 3-arm trial in NRTI-, PI-, and NNRTI- experienced HIV-1 infected subjects, to evaluate the safety, tolerability, and efficacy of different doses (400 and 800 mg on stage 1; 800 and 1200 mg on stage 2) of etravirine b.i.d. (formulation TF035) in addition to an individually optimized antiretroviral therapy by means of a 2-stage dose-escalating design for 48 weeks (initial treatment period).

Dose escalation was performed in 2 stages. In the first stage, 166 HIV-1 infected, 3-class ART-experienced subjects were randomized and treated with either placebo or etravirine 400 or 800 mg b.i.d. In the second stage, 74 subjects were randomized and treated with either placebo or etravirine 800 or 1200 mg b.i.d. Stage 2 was opened for enrollment after review of the available safety and efficacy data when 120 subjects in Stage 1 had been treated for 4 weeks or discontinued earlier, and concurrence by the Data and Safety Monitoring Board (DSMB).

Overall, 240 patients were enrolled (66 in the placebo arm; 174 in the etravirine arms). Of critical relevance is that enfuvirtide was only allowed after a protocol amendment hence its use was more frequent in Stage 2 (39.2%) when compared with Stage 1 (14.5%). Also of importance is an imbalance that was observed across arms (in stage 1 and in stage 2) regarding the use of sensitive lopinavir/ritonavir and enfuvirtide.

During the conduct of the study, an issue with the correct measure of viral load was detected. Initially, plasma viral load measurements were done using plasma preparation tubes (PPT) tubes for sample collection. During the conduct of the trial, data from other trials showed that these PPT tubes tended to yield higher HIV-1 RNA levels than EDTA tubes for HIV-1 RNA within the 50-400 copies/mL. Therefore, from April 2004 onwards, viral load was additionally determined on plasma samples from standard ethylenediaminetetra-acetic acid (EDTA) tubes at specific time points (Weeks 2, 4, 12, 24,

48, 72, 96, 120 and 144) and a possible difference in viral load due to tube type was explored. Consequently, for visits that occurred before this date, no 'standard EDTA' (further referred to as 'EDTA') data is available. For samples for which both results (PPT and EDTA) were available, the data showed that PPT results for plasma viral load were often higher than the corresponding EDTA value. This PPT bias was most apparent for the response parameters where plasma viral load levels below 400 copies/mL were assessed.

In Stage 1, no difference was noted between the treatment groups, either in the PPT analysis or the EDTA analysis. The pair-wise comparison of the LS means of the etravirine 400 mg b.i.d. and etravirine 800 mg b.i.d. groups was not statistically significant at Weeks 24 and 48. Both etravirine dose groups were not statistically significantly different from the placebo group at both time points. In Stage 2, a trend was noted to show an additional benefit of the 2 etravirine groups over placebo in the PPT analysis. An additional antiviral effect was noted for the etravirine 800 mg b.i.d. group over placebo (p=0.009) in the EDTA analysis at week 24. Of note, there were only 11 subjects in the placebo group in Stage 2 and the trial was not powered to show statistical significance vs placebo. In subgroup analyses of Stage 1 where the potency of the PI component of the underlying ART was most compromised (e.g. subjects with more than 2 primary PI mutations or not using a sensitive PI in the underlying ART), an additional antiviral effect was noted for the etravirine 800 mg b.i.d. group. It should be noted that the response rates were substantially higher with the EDTA data as compared with the PPT data for all treatment groups.

Overall, the CHMP concluded that the efficacy results of this study have been flawed by significant confounding factors (use of PPT tube for the viral load and lack of consistency with a re-test with EDTA tube, significant imbalances [enfuvirtide use, sensitive PI] across treatment arms), which preclude any reliable interpretation of the efficacy data. Therefore this study was not considered to provide any contribution to the dose selection.

Study C223

Study 223 was a randomized, controlled, partially blinded Phase IIb dose-finding study investigating etravirine (400 and 800 mg b.i.d., TF035 formulation) in HIV-1 infected subjects with documented genotypic evidence of resistance to currently available NNRTIs and with at least 3 primary PI mutations. The design of the study was as follows:

- In the control group, the ART started at baseline was a standard of care regimen consisting of at least 3 approved drugs (NRTIs and/or PIs and/or ENF in any combination).
- In the etravirine groups, the background regimen started at baseline consisted of at least 2 approved drugs containing NRTI(s) (except "new abacavir" which was excluded to avoid difficulties in determining the etiology of any symptoms of rash or hypersensitivity) and/or lopinavir/r and/or enfuvirtide in any combination.

The therapy was selected by the investigator within the frame of the protocol and based on subject's genotypic data and/or previous treatment history.

The use of a boosted protease inhibitor in the OBT was not binding in this study; if however a boosted protease inhibitor was to be used in the etravirine arms then this was lopinavir/ritonavir. It is noteworthy that the pivotal studies required the use of darunavir/ritonavir in the OBT (see below).

The primary antiviral activity parameter was the change in $\log_{10}$ plasma viral load at Week 24. The overall duration of the study was 48 weeks.

The population enrolled was advanced in HIV-infection with a mean duration of infection of about 15 years and more than 60% of patients classified in CDC class C, 50% of patients had CD4 cell count $<100/mm^3$. In addition, the population was heavily experienced as illustrated by the genotypic analysis with a high level of resistance mutations to anti-retroviral drugs. The phenotypic analyses showed a resistance to the NNRTIs nevirapine and efavirenz (whereas the strains were sensitive to etravirine) and to the PIs in particular lopinavir which is the only one allowed in the etravirine groups. Overall, the population enrolled had a median of 2 NNRTIs mutations, taking into account the extended NNRTI resistance associated mutations.

The etravirine study arms showed important imbalances compared to the control arm:

- The use of enfuvirtide that was more frequent in the etravirine arms than in the control arm (approx 63% versus 54%). Moreover, whereas the "naïve use" represented approximately half of the total use of enfuvirtide in the control arm, this proportion was much higher for the etravirine arms (60% to 90%).
- The percentage of patients with a PSS 0 in the OBT was different between the etravirine arms and the control arm (16% versus 26% respectively).

The results of this study are presented in Table 10. No statistical difference was observed between the two etravirine doses tested. The viral load change from baseline was statistically superior with both etravirine doses as compared to the control arm. However, compared to the control arm the etravirine arms were associated with an approx 0.7 log decrease in viral load, which is considered limited particularly when considering a potential for overestimation given the imbalances in the study groups.

Table 10 ANCOVA Model: LSmeans for the change in log10 viral load from baseline (NC=F) at Weeks 24 and 48 and pairwise comparison with control (ITT population)

Treatment Group ITT Population	LSmean (SE)	Difference With Control (SE)	P-Value for comparison with control[a]	Difference Between Dose Groups (SE)	P-Value for dose comparison[a]
Week 24					
Etravirine 400 mg b.id.	-1.030 (0.1495)	-0.619 (0.2085)	0.003	0.164 (0.1701)	0.337
Etravirine 800 mg b.id.	-1.194 (0.1446)	-0.782 (0.2075)	< 0.001		
Control	-0.412 (0.1925)	-	-	-	-
Week 48					
Etravirine 400 mg b.id.	-0.886 (0.1556)	-0.518 (0.2172)	0.018	0.157 (0.1771)	0.376
Etravirine 800 mg b.id.	-1.043 (0.1506)	-0.657 (0.2160)	0.002		
Control	-0.368 (0.2004)	-	-	-	-

[a]p-value for pairwise comparisons (ANCOVA including ENF in the ART and treatment group as factors, and baseline CD4 cell count and viral load as covariates. The interaction between treatment group and ENF in the ART was dropped because it was not significant at the 0.20 level).

It is noteworthy that the population was mainly composed of heavily pretreated patients at an advanced stage of the disease, hence etravirine might have been the only active substance expected to significantly carry the antiviral activity, if only combined with NRTIs. Lopinavir/ritonavir was used in approximately half of the population; the same applies for enfuvirtide. This could explain to some extent the results observed in the etravirine arms in this study. Of note that lopinavir/ritonavir was used despite being not active in the vast majority of patients treated by the combination.

These study results are not considered to impact the extrapolation of the DUET studies results to boosted protease inhibitors other than darunavir/ritonavir, such as lopinavir/ritonavir. Nevertheless, further reassurance on the extrapolation of the DUET study results is expected with the additional confirmatory study.

- Main study(ies)

Two Phase III randomized, double-blinded, placebo-controlled trials were conducted to investigate the efficacy, tolerability and safety of etravirine as part of an antiretroviral therapy including darunavir/ritonavir and an investigator-selected optimised background regimen (OBR) in HIV-1 infected subjects with limited to no treatment options:

- Study C206 (DUET-1), conducted in Argentina, Brazil, Chile, France, Mexico, Panama, Puerto Rico, Thailand, USA, and Costa Rica;
- Study 216 (DUET-2), conducted in Australia, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, The Netherlands, UK, and USA.

This duplication of the efficacy demonstration is of interest for the robustness of the analysis.

METHODS (FOR BOTH STUDIES)

Study Participants

The study population were HIV-1 infected with limited to no treatment options. The main inclusion criteria were

- age ≥ 18 years;
- plasma HIV-1 RNA > 5000 copies/mL;
- on a stable ART for at least 8 weeks at screening;
- at least 1 NNRTI resistance-associated mutation (RAM) either at screening or from historical genotype reports: A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179I/F/G, Y181C/I/V, Y188C/H/L, G190A/E/S, P225H, F227C, M230I/L, P236L, K238N/T, Y318F (adapted from the IAS-USA list, update November 2005);
- 3 or more documented primary PI mutations at screening (IAS-USA list, update November 2005).

Main exclusion criteria were

- any currently active AIDS defining illness (Category C) with the following exceptions: Stable cutaneous Kaposi's Sarcoma unlikely to require any form of systemic therapy during the trial period or Wasting syndrome due to HIV infection;
- chronic hepatitis B and/or C with aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN).

Of note that subjects co-infected with chronic hepatitis B or C were allowed to enter the trial if their condition was clinically stable and was not expected to require treatment during the trial period.

Treatments

During the screening period (maximum of 6 weeks) current ART regimen to baseline was continued.

With the start of the treatment period for at least 48 weeks, the following was administered:

Etravirine group:

- Etravirine 200 mg b.i.d.: administered as 2 tablets b.i.d.;
- Darunavir/ritonavir 600/100 mg b.i.d.: administered as 2 tablets darunavir and 1 capsule ritonavir b.i.d.;
- OBR: at least 2 ARV drugs: NRTI(s) with or without enfuvirtide.

Placebo group:

- Placebo: administered as 2 tablets b.i.d.;
- Darunavir/ritonavir 600/100 mg b.i.d.: administered as 2 tablets darunavir and 1 capsule ritonavir b.i.d.;
- OBR: at least 2 ARV drugs: NRTI(s) with or without enfuvirtide.

De novo use of ENF was limited to a maximum of 40% of the overall trial population. There was neither restriction on the total number of ARVs from the allowed classes nor a requirement for sensitivity towards the ARVs in the OBR. Investigators were however encouraged to maximize the use of sensitive ARVs in the OBR.

Etravirine or placebo and darunavir/ritonavir were taken orally in the morning and in the evening immediately following a meal. Etravirine was administered in the commercial formulation (F060). The OBR was taken according to the manufacturer's prescribing information.

The treatment period was followed by a 4-week post-treatment follow-up period.

Objectives

The primary objective was to show the superiority of etravirine compared to placebo as part of an ART containing darunavir/ritonavir and a-selected OBR, in the proportion of subjects with <50 copies/mL) at Week 24 in ARV-experienced HIV-1 infected subjects.

Secondary objectives included virologic, immunologic and clinic response.

Outcomes/endpoints

Primary endpoint was the proportion of subjects with an undetectable plasma viral load i.e. <50 copies/mL at week 24 according the time to loss of virologic response (TLOVR) algorithm.

A difference of 20% was assumed between the etravirine group and the placebo group in the situation whereno *de novo* enfuvirtide was used. The assumption was made that in subjects receiving DRV/rtv and *de novo* ENF, no added benefit of TMC125 could be demonstrated.

Sample size

Sample size calculations were based on the expected response rate at Week 24, also considering the impact of enfuvirtide use, as well as the significance level (5%, 2-sided).

For DUET-1, 1220 subjects were screened, and 612 subjects were randomised and treated (304 etravirine, 308 placebo). For DUET-2, 954 subjects were screened, and 591 subjects were randomised and treated (295 etravirine, 296 placebo).

Randomisation

Eligible subjects were randomized to either the etravirine arm or the placebo arm in a 1:1 ratio. The randomization was stratified by:

- the intended use of enfuvirtide in the underlying ART (using enfuvirtide *de novo*, re-using enfuvirtide, or not using enfuvirtide),
- previous use of darunavir (yes, no),
- screening plasma viral load (< or ≥ 30 000 HIV-1 RNA copies/mL).

Blinding (masking)

The study was conducted double-blinded.

Statistical methods

The intent-to-treat (ITT) population was defined as all randomized subjects who began treatment, regardless of their compliance with the protocol. The ITT population was used as primary population for the entire analysis.

An on-protocol efficacy population (i.e., ITT subjects with no major efficacy-related protocol violations), and the on-protocol pharmacokinetic population (i.e. ITT subjects with no major pharmacokinetic-related protocol violations) were only used for analysis if they excluded at least 10% of the number of subjects in the ITT population.

As primary analysis method, the Cochran-Mantel-Haenszel (CMH) test controlling for the stratification factors (use of ENF in the underlying ART, previous use of darunavir, and baseline plasma viral load) was applied to test the difference between the treatment groups at Week 24.

The primary efficacy parameter is the proportion of subjects with undetectable plasma viral load values (< 50 copies/mL) at Week 24. The FDA TLOVR imputation algorithm was used in the calculation of this proportion:

- 2 consecutive values below the threshold were needed to count as response. Once a subject

was a responder, 2 consecutive values above the threshold needed to be observed in order to be determined a non-responder (rebound). Once a subject was determined as a non-responder, following values below the threshold were not counted as a response.

- Intermittent missing values were imputed as response if the preceding value was a response and the missing value was followed by a response value.
- Subjects who discontinued the trial were considered as non-responders after discontinuation.

The primary analysis was done when all subjects had been treated for at least 24 weeks or discontinued earlier. All available data were included in the analysis. Additionally, an updated analysis will be performed once all subjects have been treated for 48 weeks. A final analysis of the trial will be performed once all subjects have completed the optional treatment extension period, including the follow-up visit (if applicable). A pooled analysis for efficacy, safety and pharmacokinetics will be done (at Week 24 and at time points where the individual trials are also analyzed) combining the data of C206 with C216.

Several DSMB analyses to describe the overall safety are being performed throughout the trial.

RESULTS

Participant flow

The participant flow is outlined in Figures 1 and 2.

Figure 1 Patient flow in study C206 (DUET-1)

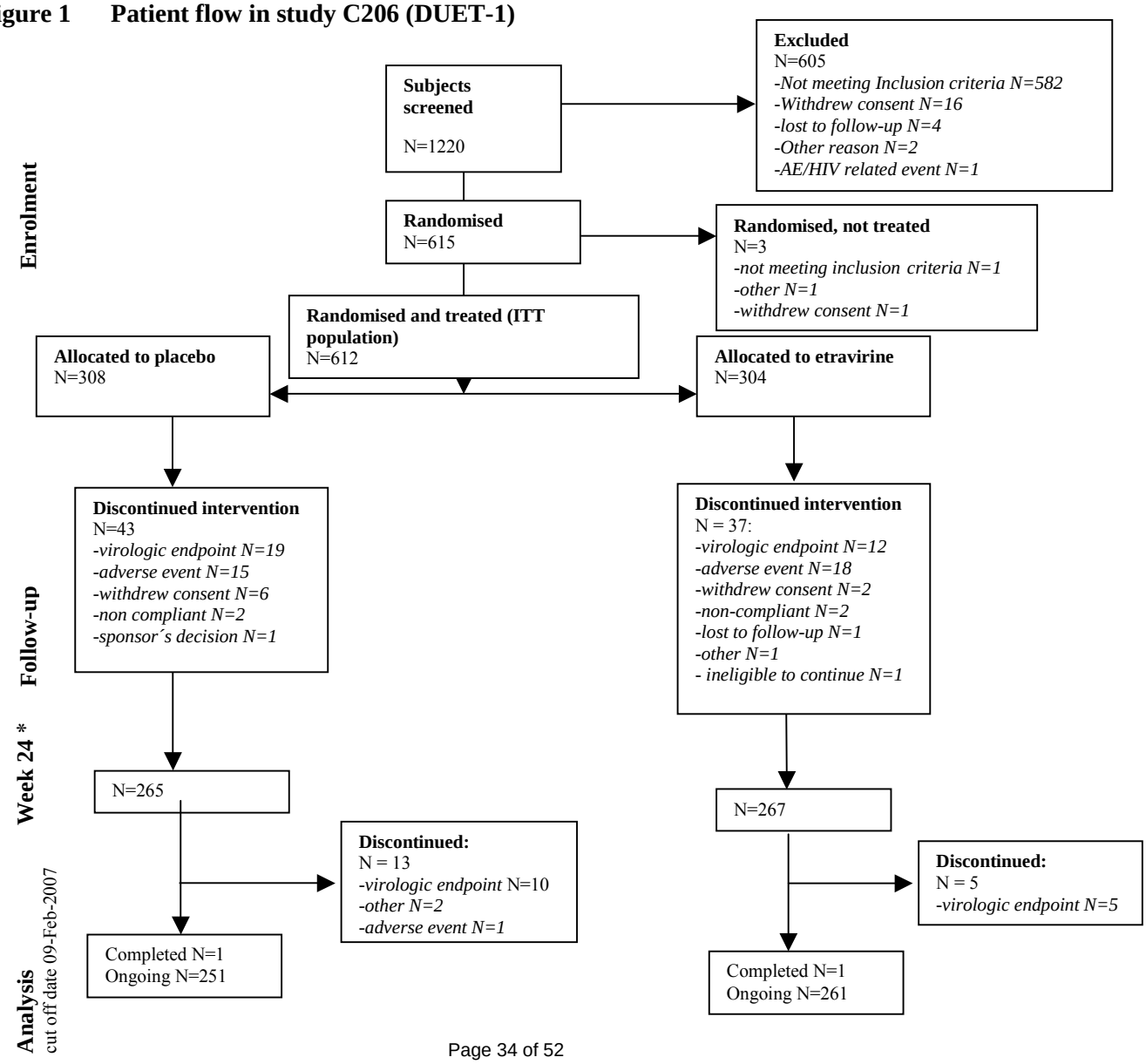
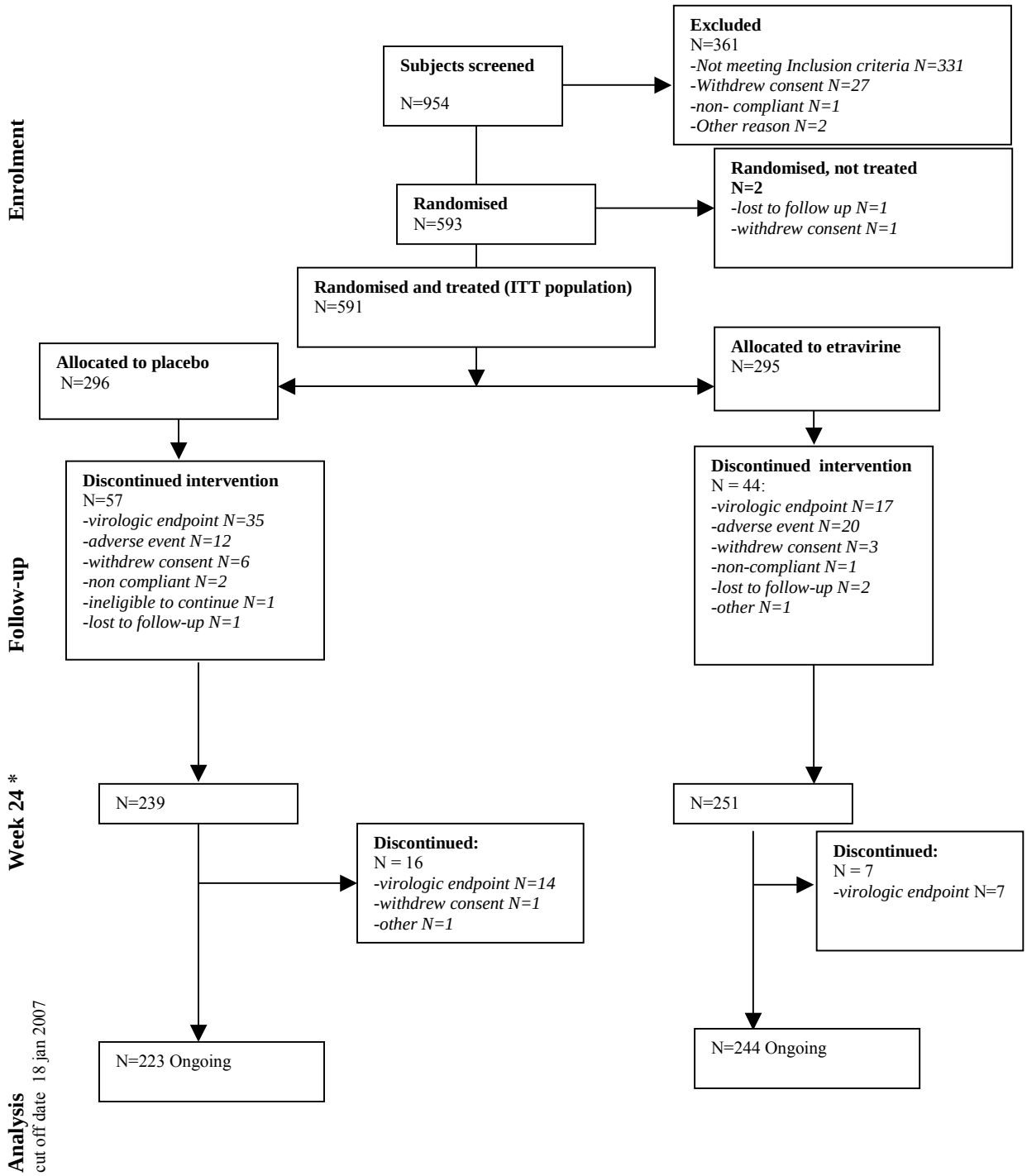


Figure 2 Patient flow in study C216 (DUET-2)



Recruitment

For study C206, the first visit was on 10 November 2005, and the last visit (relevant for the 24-week data) on 9 February 2007.

For study C216, the first visit was on 31 October 2005, and the last visit (relevant for the 24-week data) on 18 January 2007.

Conduct of the study

Five protocol amendments were made during the conduct of the study (until the 24 week analysis).

Protocol deviations were relatively rare and evenly distributed across study arms; they concern mainly forbidden medication during the treatment period and are not considered relevant for the final analysis.

Baseline data

Baseline and demographic data is displayed in Tables 11 and 12.

Table 11 Demographic and baseline characteristics of subjects in study C206 (DUET-1)

Baseline Characteristics	Placebo N = 308	Etravirine N = 304	All Subjects N = 612
Demographic Data			
Gender, n (%)			
Female	44 (14.3)	41 (13.5)	85 (13.9)
Male	264 (85.7)	263 (86.5)	527 (86.1)
Age: median (range), years	45.0 (18-72)	45.0 (18-67)	45.0 (18-72)
Weight[a]: median (range), kg	70.0 (34-123)	71.0 (36-131)	70.6 (34-131)
BMI[a]: median (range), kg/m^2	23.0 (13-40)	23.1 (15-40)	23.1 (13-40)
Ethnic origin[b], n (%)			
Caucasian	189 (64.7)	187 (64.7)	376 (64.7)
Hispanic	42 (14.4)	41 (14.2)	83 (14.3)
Black	35 (12.0)	39 (13.5)	74 (12.7)
Other	23 (7.9)	20 (6.9)	43 (7.4)
Asian	3 (1.0)	2 (0.7)	5 (0.9)
Baseline Disease Characteristics			
Viral load[a]: median (range), copies/mL	77,000.0 (227-3,030,000)	67,850.0 (479-1,740,000)	75,200.0 (227-3,030,000)
Log_{10} viral load[a]: median (range), copies/mL	4.9 (2-7)	4.8 (3-6)	4.9 (2-7)
CD4 cell count[a]: median (range), 10^6 cells/L	109.0 (1-694)	99.0 (1-789)	106.0 (1-789)
Duration of known HIV infection[c]: median (range), years	13.3 (5-26)	13.4 (4-25)	13.3 (4-26)
CDC Category, n (%)			
Category A	59 (19.2)	69 (22.7)	128 (20.9)
Category B	54 (17.5)	51 (16.8)	105 (17.2)
Category C	195 (63.3)	184 (60.5)	379 (61.9)
HBV – HBsAg Positive, n (%)	19 (6.2)	22 (7.2)	41 (6.7)
Active HCV infection, n (%)	12 (4.3)	12 (4.3)	24 (4.3)
Hepatitis B and/or C co-infection	31 (11.1)	34 (12.1)	65 (11.6)

N = number of subjects, n = number of subjects; [a] Baseline values were imputed with screening values if no data at baseline were available; [b] For ethnic origin: 31 subjects are not included in the denominator for race percentages because local regulations in some countries preclude collection of these data and are not in this table; [c] At the time of screening.

Table 12 Demographic and baseline characteristics of subjects in study C216 (DUET-2)

Baseline Characteristics	Placebo N = 296	Etravirine N = 295	All Subjects N = 591
Demographic Data			
Gender, n (%)			
Male	271 (91.6)	276 (93.6)	547 (92.6)
Female	25 (8.4)	19 (6.4)	44 (7.4)
Age: median (range), years	45.0 (20-69)	46.0 (31-77)	46.0 (20-77)
Weight[a]: median (range), kg	72.0 (45-137)	74.0 (41-115)	72.5 (41-137)
BMI[a]: median (range), kg/m^2	22.9 (15-47)	23.4 (14-34)	23.2 (14-47)
Ethnic origin[b], n (%)			
Caucasian	187 (75.7)	186 (76.5)	373 (76.1)
Black	35 (14.2)	31 (12.8)	66 (13.5)
Hispanic	24 (9.7)	19 (7.8)	43 (8.8)
Asian	0	5 (2.1)	5 (0.8)
Other	1 (0.4)	2 (0.8)	3 (0.6)
Baseline Disease Characteristics			
Viral load[a]: median (range), copies/mL	61450.0 (177-2,110,000)	65300.0 (977-7,030,000)	64500.0 (177-7,030,000)
Log_{10} viral load[a]: median (range), copies/mL	4.8 (2-6)	4.8 (3-7)	4.8 (2-7)
CD4 cell count[a]: median (range), 10^6 cells/L	108.0 (0-912)	100.0 (1-708)	105.0 (0-912)
Duration of known HIV infection[c]: median (range), years	15.1 (5-26)	14.5 (3-25)	14.9 (3-26)
CDC Category, n (%)			
Category A	71 (24.0)	57 (19.3)	128 (21.7)
Category B	63 (21.3)	76 (25.8)	139 (23.5)
Category C	162 (54.7)	162 (54.9)	324 (54.8)
HBV – HBsAg Positive, n (%)	19 (6.4)	19 (6.4)	38 (6.4)
Active HCV infection, n (%)	20 (7.1)	20 (7.0)	40 (7.1)
Hepatitis B and/or C co-infection	36 (12.8)	38 (13.3)	74 (13.1)

N = number of subjects, n = number of subjects; [a] Baseline values were imputed with screening values if no data at baseline were available; [b] For ethnic origin: 101 subjects are not included in the denominator for race percentages because local regulations in some countries preclude collection of these data and are not in this table; [c] At the time of screening.

The population enrolled in these studies were heavily pre-treated and at an advanced stage of the disease (60% being classified in CDC category C, median viral load approx 4.8 log10 copies/ml and approx 100/mm3 median CD4). A limited number of women were included (<150) as well as patients with HBV and/or HCV co-infection (<150). Clade B accounted for about 95% of all clades at baseline and only a very small number of subjects had infection with other individual clades, thus precluding any valid efficacy analysis by clade.

In line with disease status of the population, previous use of ARVs was extensive and well balanced between the etravirine and placebo arms of both studies. Most of the subjects had been previously exposed to ≥3 PIs and ≥3 NRTIs. Previous use of enfuvirtide was reported for about 40% of subjects in each combined treatment group (placebo or etravirine). *De novo* use of enfuvirtide during the treatment period was reported for about 25% of subjects in each combined treatment arm.

Mutations at codons 181 and 179 were reported at baseline for over 30% of subjects, with no differences between the studies. Mutations at codons 101 and 103 were present in about 20% and 35%, respectively, at baseline. FCs over 10 for etravirine were reported at baseline (in brackets) for viral strains with mutations 181V (30), 181I (83), 179F (23-41), 101P (18), 103H (13) and 190S (12).

Baseline phenotypic sensitivity to at least 1 protease inhibitor was 77.5% of all subjects in DUET-1 and 75% of all subjects in DUET-2. Overall sensitivity to darunavir was 63%, with similar distribution of FC <10 values for all single and combined treatment groups. The baseline phenotypic sensitivity to NRTIs was particularly poor as assessed through virco®TYPE, as there were virtually no effective

marketed NRTIs for the vast majority of subjects. As this finding was also well balanced in each combined treatment group, along with the reported baseline phenotypic sensitivity to PIs, over 50% of subjects in the placebo combined treatment arm were treated with combinations with low expectation of efficacy (darunavir/ritonavir + enfuvirtide or even darunavir/ritonavir at monotherapy).

Numbers analysed

The primary population for the efficacy analysis was the ITT population. No on-protocol efficacy analysis was performed because less than 10% of subjects had efficacy related major protocol deviations. The primary analysis was conducted when all subjects were treated for at least 24 weeks or discontinued earlier.

Study C206 (DUET-1):

- In total, 612 subjects were randomized and treated, of which 308 were in the placebo group and 304 in the etravirine group.
- Thirteen percent of the subjects discontinued the trial before (or at) Week 24, 14.0% in the placebo group and 12.2% in the etravirine group.
- At the analysis cut-off date (09-Feb-2007), 98 (16.0%) subjects had prematurely discontinued the trial, 56/308 (18.2%) in the placebo group and 42/304 (13.8%) in the etravirine group. Reaching a virologic endpoint and AE/HIV related events were the most common reasons for trial discontinuation in both treatment groups. The duration of exposure to the investigational medication was similar in both treatment groups, and treatment compliance was very good.

Study C216 (DUET-2):

- 591 subjects were randomized and treated in this ongoing Phase III trial, of which 296 were in the placebo group and 295 in the etravirine group.
- Seventeen percent of the subjects discontinued the trial before (or at) Week 24, 19.3% in the placebo group and 14.9% in the etravirine group.
- At the analysis cut-off date (18-Jan-2007) 124 (21.0%) subjects had prematurely discontinued the trial, 73/296 (24.7%) in the placebo group and 51/295 (17.3%) in the etravirine group. Reaching a virologic endpoint was the most common reason for trial termination in both treatment groups. More placebo subjects 49/296 (16.6%) discontinued for this reason compared to etravirine-treated subjects (8.1%), whereas the proportion of subjects discontinuing for AEs was 4.1% in the placebo group compared with 6.8% in the etravirine group.

Outcomes and estimation

The virologic response of patients in both studies is tabulated in Table 13.

Table 13 Summary of efficacy response at Week 24 in studies C206 and C216 (ITT population)

	DUET-1		DUET-2		Pooled	
Virologic Response Data (TLOVR)	**Placebo**	**Etravirine**	**Placebo**	**Etravirine**	**Placebo**	**Etravirine**
n (%)	N = 308	N = 304	N = 296	N = 295	N=604	N=599
Viral Load < 50 copies/mL	119 (38.6)	170 (55.9)	129 (43.6)	183 (62.0)	248 (41.1)	353 (58.9)
Non-Response Reason						
Virologic failure:	168 (54.5)	110 (36.2)	153 (51.7)	86 (29.2)	321 (53.1)	196 (32.7)
Rebound (Loss of Response)	12 (3.9)	14 (4.6)	9 (3.0)	7 (2.4)	21 (3.5)	21 (3.5)
VL < 400 copies/mL at W24	8 (2.6)	11 (3.6)	4 (1.4)	7 (2.4)	12 (2.0)	18 (3.0)
VL ≥ 400 copies/mL at W24	3 (1.0)	3 (1.0)	5 (1.7)	0	8 (1.3)	3 (0.5)
Discontinued due to VF before W24	1 (0.3)	0	0	0	1 (0.2)	0 (0.0)
Never suppressed (Not Responding)	156 (50.6)	96 (31.6)	144 (48.6)	79 (26.8)	300 (49.7)	175 (29.2)
VL< 400 copies/mL at W24	31 (10.1)	44 (14.5)	26 (8.8)	31 (10.5)	57 (9.4)	75 (12.5)
VL ≥ 400 copies/mL at W24	124 (40.3)	51 (16.8)	113 (38.2)	47 (15.9)	237 (39.2)	98 (16.4)
Discontinued due to VF before W24	1 (0.3)	1 (0.3)	5 (1.7)	1 (0.3)	6 (1.0)	2 (0.3)
Death	6 (1.9)	4 (1.3)	4 (1.4)	4 (1.4)	10 (1.7)	8 (1.3)
Discontinuation due to AE	7 (2.3)	13 (4.3)	4 (1.4)	17 (5.8)	11 (1.8)	30 (5.0)
Discontinuation due to other reasons	8 (2.6)	7 (2.3)	6 (2.0)	5 (1.7)	14 (2.3)	12 (2.0)

In both studies, the percent of patients achieving an undetectable viral load (<50 copies/ml) was higher in the etravirine group than in the placebo group (+ 20% approximately). This was in line with the assumptions when designing the studies. The difference in virologic response rate (17.3% and 18.4% in DUET-1 and DUET-2, respectively) was mainly due to a higher proportion of subjects in the placebo group (50.6% and 48.6%) as compared to the etravirine group (31.6% and 26.8%) that never reached a suppressed viral load by Week 24. In contrast, slightly more subjects in the etravirine group (4.3% and 5.8%) than in the placebo group (2.3% and 1.4%) discontinued for adverse events up to Week 24.

The primary Cochran-Mantel-Haenszel (CMH) controlling for previous use of darunavir (yes, no), and baseline plasma viral load (< 30000, ≥ 30000 HIV-1 RNA copies) for the between-group comparison on the TLOVR imputed virologic response (viral load < 50 copies/mL) data at Week 24 was done in the two enfuvirtide strata separately because the p-value of the interaction (Breslow-Day test) was significant in both studies demonstrating the existence of a statistical interaction between use of enfuvirtide and etravirine. The results are shown in Tables 14 and 15.

Table 14 Primary efficacy analysis of study C206 (ITT population)

	***De novo* ENF**		**Not *de novo* ENF**	
Primary Statistical Analysis	**Placebo N = 79**	**Etravirine N = 74**	**Placebo N = 229**	**Etravirine N = 230**
Response rate n (%)	44 (55.7)	44 (59.5)	75 (32.8)	126 (54.8)
P-value vs placebo[a]	0.7935		< 0.0001	

[a]p-value for comparisons with placebo (Hochberg adjusted p-value)

Table 15 Primary efficacy analysis of study C216 (ITT population)

	***De novo* ENF**		**Not *de novo* ENF**	
Primary Statistical Analysis	**Placebo N = 81**	**Etravirine N = 79**	**Placebo N = 215**	**Etravirine N = 216**
Response rate n (%)	55 (67.9)	58 (73.4)	74 (34.4)	125 (57.9)
P-value vs placebo[a]	0.3838		< 0.0001	

[a]p-value for comparisons with placebo (Hochberg adjusted p-value)

In the "not *de novo* ENF" main subgroup, etravirine is shown (p<0.0001) to be statistically superior to

the placebo arm at Week 24 (54.8% and 32.8% in the etravirine and placebo groups of DUET-1, respectively; 57.9% and 34.4% in the etravirine and placebo groups of DUET-2, respectively;). Of note, based on individual 48 weeks study results, the statistical superiority was also achieved in the subgroup of *de novo* ENF in DUET 2 study. This will have to be further analysed within the pooled efficacy analysis to be provided.

The results of secondary virologic response parameters at Week 24 are presented in Tables 16 and 17. The data are consistent with the one of the primary analysis.

Table 16 Secondary efficacy analysis of study C206 (ITT population)

Secondary Statistical Analysis Specification	***De novo* ENF**		**Not *de novo* ENF**	
	Placebo N = 79	**Etravirine N = 74**	**Placebo N = 229**	**Etravirine N = 230**
CMH Test				
Viral Load < 400 copies/mL Response rate, n (%)	58 (73.4)	74 (83.8)	100 (43.7)	162 (70.4)
P-value vs placebo[a]	0.1218		< 0.0001	
Decrease > 1.0 Log_{10} in Viral Load Response rate, n (%)	66 (83.5)	65 (87.8)	112 (48.9)	178 (77.4)
P-value vs placebo[a]	0.4657		< 0.0001	
Logistic Regression Model				
Viral Load < 400 copies/mL				
Predicted response rate [95% CI][b]	75.2 [64.5;83.5]	84.9 [75.0;91.3]	43.3 [36.9;49.9]	70.7 [64.4;76.3]
Difference with placebo [95% CI][b]	9.7 [-3.0;22.3]		27.5 [18.7;36.2]	
P-value vs placebo (ENF strata)	0.1322		< 0.0001	
P-value vs placebo (overall)	0.0001			
Decrease > 1.0 Log_{10} in Viral Load				
Predicted response rate [95% CI][b]	83.9 [74.1;90.4]	88.0 [78.5;93.7]	48.9 [42.4;55.3]	77.4 [71.5;82.3]
Difference with placebo [95% CI][b]	4.1 [-6.9;15.2]		28.5 [20.1;37.0]	
P-value vs placebo (ENF strata)	0.4619		< 0.0001	
P-value vs placebo (overall)	0.0015			

N = number of subjects, n = number of observations; [a] p-value from CMH test (Hochberg adjusted p-value); [b] predicted estimates from logistic regression model with covariates baseline viral load and factors ENF and treatment and interaction term ENF* treatment

Table 17 Secondary efficacy analysis of study C216 (ITT population)

Secondary Statistical Analysis Specification	*De novo* ENF		Not *de novo* ENF	
	Placebo N = 81	**Etravirine N = 79**	**Placebo N = 215**	**Etravirine N = 216**
CMH Test				
Viral Load < 400 copies/mL Response rate, n (%)	63 (77.8)	68 (86.1)	96 (44.7)	153 (70.8)
P-value vs placebo[a]	0.2042		< 0.0001	
Decrease > 1.0 Log_{10} in Viral Load Response rate, n (%)	69 (85.2)	70 (88.6)	106 (49.3)	165 (76.4)
P-value vs placebo[a]	0.6437		< 0.0001	
Logistic Regression Model				
Viral Load < 400 copies/mL				
Predicted response rate [95% CI][b]	78.4 [68.1;86.1]	87.3 [78.2;92.9]	43.7 [37.0;50.6]	72.2 [65.7;77.8]
Difference with placebo [95% CI][b]	8.8 [-2.8; 20.5]		28.5 [19.5; 37.4]	
P-value vs placebo (ENF strata)	0.1365		< 0.0001	
P-value vs placebo (overall)	0.0001			
Decrease > 1.0 Log_{10} in Viral Load				
Predicted response rate [95% CI][b]	85.4 [75.9; 91.5]	89.1 [80.2; 94.3]	48.9 [42.2; 55.6]	77.0 [70.9; 82.1]
Difference with placebo [95% CI][b]	3.7 [-6.7; 14.1]		28.1 [19.3; 36.8]	
P-value vs placebo (ENF strata)	0.4839		< 0.0001	
P-value vs placebo (overall)	0.0023			

N = number of subjects, n = number of observations; [a] p-value from CMH test (Hochberg adjusted p-value); [b] predicted estimates from logistic regression model with covariates baseline viral load and factors ENF and treatment and interaction term ENF* treatment

With regard to plasma viral load, an approximately 1 log difference in viral load was observed between etravirine and placebo in the subgroup of patients not using *de novo* enfuvirtide.

The increase in absolute and % CD4 cell count was higher in the etravirine group than in the placebo group at all time points (see Table 18).

Table 18 CD4 cell count at week 24 in studies C206 and C216

	C206		**C216**	
	Placebo	Etravirine	Placebo	Etravirine
Absolute (cells/µL)	+ 64.4	+89.0	+ 65.5	+ 78.1
%	+ 2.6%	+ 3.5%	+ 2.9%	+ 3.7%

Of note, the results of statistical analyses regarding the mean increase in CD4 cells are different for DUET-1 and DUET-2. In both studies, the increase in CD4 cell is superior in the etravirine arm than in the placebo arm in the not *de novo* enfuvirtide use subgroup. Moreover, in DUET-1 but not in DUET-2, the increase was also significantly superior in the *de novo* enfuvirtide group (absolute value) and in the overall population.

With regard to clinical endpoints, in line with the virologic response the number of patients experiencing an AIDS defining illness or death is higher in the placebo arm than in the etravirine arm, this is especially noticeable in the subgroup not using enfuvirtide *de novo*.

Ancillary analyses

A sensitivity analysis was performed that provides further robustness in the efficacy demonstration. The same applies for the consistency of the analyses performed on the secondary endpoints.

Impact of baseline NNRTI genotype and phenotype on virologic response

Various analyses have been performed to investigate the impact of genotypic and phenotypic parameters on the virologic response to etravirine. The results are summarised in the section "Clinical aspects, Pharmacodynamics".

- Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis of the efficacy results of the pivotal studies C206 and C216 was performed. The results of the primary efficacy statistical analysis of the pooled data are shown in Table 19. Like for the individual studies, there was a statistically significant interaction (p = 0.069, Breslow Day test) between treatment and enfuvirtide hence the primary statistical analysis was performed separately in the two enfuvirtide strata (*de novo* ENF use and not *de novo* ENF use).

Table 19 Primary efficacy analysis of the pooled data of studies C206 and C216 (ITT population)

	Pooled DUET Trials			
	***De novo* ENF**		**Not *de novo* ENF**	
	Placebo N = 160	**Etravirine N = 153**	**Placebo N = 444**	**Etravirine N = 446**
Observed response rates	61.9 %	66.7 %	33.6 %	56.3 %
p-value vs placebo Hochberg adjusted p-value*	0.427		< 0.0001	

*CMH test controlling for baseline viral load and previous darunavir use

- Supportive study(ies)

Available data from other controlled or uncontrolled studies is of limited use to further support the efficacy data obtained with the two pivotal studies. However, one study appears to be relevant for clinical use although being conducted with a different objective than the pivotal studies, and is therefore discussed below.

Study 227 was a randomized, active controlled, open label trial to investigate the efficacy and tolerability of etravirine in HIV-1 infected subjects, who are PI-naïve and with documented genotypic evidence of NNRTI resistance from previous NNRTI use. The objective was to evaluate the antiviral activity of etravirine 800 mg b.i.d. (formulation TF035) as part of an ART containing two NRTIs. The comparator was an investigator-selected protease inhibitor in combination with two investigator-selected NRTIs. This design could explore the potential use of etravirine as a PI sparing strategy in order to delay the introduction of a protease inhibitor in the therapeutic management of patients with NNRTIs resistance.

The primary endpoint was pproportion of subjects with plasma HIV 1 RNA levels < 50 copies/mL at 24 weeks. However, for the patients who reached 12 weeks of treatment at time of study discontinuation, the week 12 virologic response was greater in the control-PI arm (-2.2 $\log_{10}$ copies/ml from baseline; n=53) compared to the etravirine arm (-1.4 $\log_{10}$ copies/ml from baseline; n=40). This difference between treatment arms was statistically significant. Due to this early identification of suboptimal virologic response in the etravirine treated subjects, the recruitment was stopped and etravirine treated patients were recommended to switch to an investigator-selected PI-containing ARV regimen.

Due to these results it is important that etravirine should not be used in combination with only NRTIs in patients who have experienced virological failure with a first line NRTI + NNRTI-containing regimen. The results are included in SmPC section 5.1 since they are considered clinically relevant, and they reinforce the indication wording in SmPC section 4.1 that etravirine is to be used with boosted protease inhibitors.

Clinical safety

The evaluation of the safety and tolerability profile of etravirine is based on data from healthy volunteers and HIV-1 infected subjects from completed trials, as well as data from HIV-1 infected subjects from ongoing trials.

With regard to Phase I/IIa studies a total of 1093 healthy subjects and 144 HIV-infected subjects were enrolled. One healthy subject died 3 days after a single dose of etravirine. The cause of death was considered by the investigator as unknown, possibly cardiovascular, and doubtfully related to etravirine.

In the multiple dose Phase I trials, 15.5% of healthy subjects (vs. 14.5% in placebo group) developed rash during treatment with etravirine. Three of the 4 grade 3 rashes occurred in a single-dose Phase I healthy subjects trial. The skin events were diagnosed as erythema multiforme (2 subjects) or atypical bullous dermatitis (1 subject) and were rated grade 3 in severity. Thereafter, 1 additional grade 3 morbilliform rash case was reported in a multiple dose Phase I trial. Skin events accounted for the highest proportion of healthy volunteers who discontinued because of AEs in the multiple-dose Phase I trial (5.3%) and there was an apparent trend for higher incidence of rash in women compared with men.

The following describes the safety profile of etravirine particularly based on the data from the pivotal Phase III studies.

- Patient exposure

In total, 1041 subjects were exposed to etravirine treatment across Phase IIb and III trials; 861 subjects for at least 24 weeks and 279 subjects for at least 48 weeks.

In the pooled DUET trials, 548 (91.5%) subjects in the etravirine group and 556 (92.1%) subjects in the placebo group were treated for at least 24 weeks. The median duration of treatment was 30.0 weeks for etravirine treated subjects and 29.1 weeks for placebo control; total subject years of exposure was 357.7 for the etravirine subjects and 359.5 for placebo treated subjects.

- Adverse events

The most common AEs (in at least 10.0% of the etravirine-treated subjects) observed with etravirine in the DUET trials were diarrhoea (15.0% vs. 20.4% in the placebo group), nausea (13.9% vs. 11.1%), and rash (individual term, 10.0% vs. 5.5%).

Rash (any type), grouping all rash-related terms, was reported in 17.0% of subjects in the etravirine group compared to 9.4% in the placebo group.

The most commonly reported ADRs of at least grade 2 reported with etravirine treatment (Table 20) were rash (any type), reported for 9.0% of etravirine-treated subjects and for 3.1% of placebo treated subjects, diarrhoea (5.2% and 9.6%), nausea (4.7% and 3.5%), and hypertriglyceridemia (4.7% and 3.0%).

Table 20 Adverse drug reactions at least grade 2 in at least 2% of etravirine treated subjects (pooled DUET analysis)

n (%)	DUET 1		DUET 2		Pooled DUET	
	Placebo N = 308	Etravirine N = 304	Placebo N = 296	Etravirine N = 295	Placebo N = 604	Etravirine N = 599
Gastrointestinal disorders						
Diarrhoea	33 (10.7)	9 (3.0)	25 (8.4)	22 (7.5)	58 (9.6)	31 (5.2)
Nausea	12 (3.9)	11 (3.6)	9 (3.0)	17 (5.8)	21 (3.5)	28 (4.7)
Abdominal pain	10 (3.2)	8 (2.6)	5 (1.7)	10 (3.4)	15 (2.5)	18 (3.0)
Vomiting	8 (2.6)	5 (1.6)	4 (1.4)	9 (3.1)	12 (2.0)	14 (2.3)
Metabolism and nutrition disorders						
Hypertriglyceridaemia	9 (2.9)	9 (3.0)	9 (3.0)	19 (6.4)	18 (3.0)	28 (4.7)
Hypercholesterolaemia	5 (1.6)	9 (3.0)	8 (2.7)	12 (4.1)	13 (2.2)	21 (3.5)
Skin and subcutaneous tissue disorders						
Rash (any type)[#]	11 (3.6)	32 (10.5)	8 (2.7)	22 (7.5)	19 (3.1)	54 (9.0)
Nervous system disorders						
Neuropathy peripheral	5 (1.6)	8 (2.6)	6 (2.0)	9 (3.1)	11 (1.8)	17 (2.8)
Headache	19 (6.2)	9 (3.0)	6 (2.0)	7 (2.4)	25 (4.1)	16 (2.7)
Blood and lymphatic system disorders						
Anaemia	9 (2.9)	10 (3.3)	13 (4.4)	11 (3.7)	22 (3.6)	21 (3.5)
General disorders and administration site conditions						
Fatigue	11 (3.6)	7 (2.3)	13 (4.4)	13 (4.4)	24 (4.0)	20 (3.3)
Vascular disorders						
Hypertension	7 (2.3)	10 (3.3)	6 (2.0)	7 (2.4)	13 (2.2)	17 (2.8)

N = Number of subjects; n = number of subjects with observations; [#] Grouped term including any type of rash

Of the 1041 subjects treated with etravirine in the Phase IIb and III trials, 277 were treated for more than 48 weeks, with median treatment duration of 119.6 weeks.

The incidence of AEs, including rash, tended to decrease with long-term dosing, except for psychiatric AEs which were similar in incidence in the 2 treatment phases (i.e. in the first 48 weeks and in the period after Week 48), and the coronary disorder events which showed a higher incidence in the period after Week 48 (3.2%) than in the first 48 weeks (1.8%).

In the phase III rollover trial (C217), patients from the etravirine continued treatment arm had more nervous system disorders than patients from the etravirine *de novo* arm (23.1% vs 12.0%).

- Serious adverse event/deaths/other significant events

Skin events

Rash was reported in the DUET trials with a higher incidence in the etravirine group compared to the placebo group (17.0% vs 9.4%) (p=0.0001 vs placebo; Fisher's exact test). Rashes during etravirine treatment mostly emerged during the first 4 weeks of treatment with a median time to onset of 12 days and resolved with continued treatment (median duration of 11 days).

Eight (1.3%) subjects in the etravirine group developed a grade 3 rash (none in the placebo group). There were no grade 4 rashes. No cases of erythema multiforme, SJS or toxic epidermal necrolysis were observed in the etravirine group of the DUET trials.

In addition to the cluster of grade 3 atypical rashes in one of the early Phase I trials, there was 1 case of SJS reported in the EAP and 1 case of erythema multiforme reported in Phase IIb trials.

Forty-eight subjects enrolled in the DUET trials with history of rash were treated with etravirine. Of these, 9 developed mild to moderate rash while on etravirine, 1 subject developed grade 3 rash and 3

discontinued as a result of rash.

The incidence of rashes in the etravirine-treated subjects was higher in patients with a history of NNRTI-associated rash compared to patients without such history (13.5% versus 8.8%, respectively, for grade 2 rash, and 2.7% versus 1.0%, respectively, for grade 3 rash). Moreover, permanent discontinuations of etravirine were also more frequent in subjects with history of NNRTI-associated rash compared to patients without such history (5.4% vs 2.0%, respectively).

Regarding the low number of patients exposed to etravirine, a non significant result may be due to a lack of power in the logistic regression analysis, and an increase of the risk of rash in patients with a history of NNRTI-associated rash cannot be excluded at this stage. Moreover, no conclusion may indeed be done in case of history of a severe skin reaction with an NNRTI (i.e. EM, SJS or TEN).

A precautionary statement is included in the SmPC, and a particular survey will be provided in the PSURs.

Neuropsychiatric events

In the pooled DUET trials, neuropsychiatric AEs of interest were reported by 25.4% of subjects in the etravirine group, which was similar to the incidence in the placebo group (30.1%) ($p = 0.0714$ vs. placebo; Fisher's exact test).

In 2 (0.3%) subjects these symptoms were grade 3 in severity in the etravirine group compared with 12 (2.0 %) in the placebo group. There were no grade 4 events in the etravirine group (vs. 1 subject (0.2%) in the placebo group). In DUET trials, 1 (0.2%) subject discontinued etravirine therapy because of neuropsychiatric symptoms.

Hepatic events

In toxicology studies, the liver was identified as target organ following etravirine dosing in mice and dogs.

In the pooled DUET trials, the incidence of hepatic events was comparable to placebo (5.3% vs. 5.1% in the placebo group). The most common hepatic AEs in subjects that initiated treatment with etravirine were related to increases in hepatic enzymes (3.5% vs. 3.0% in the placebo group).

Hepatitis B and/or C co-infection:
In order to collect safety data in HIV-1 infected subjects co-infected with hepatitis B and/or C virus, it was decided to allow recruitment of these subjects in the Phase IIb and DUET trials, if their condition was clinically stable and did not require treatment.

There was a trend for a higher incidence of hepatic AEs (SOC hepatobiliary disorders and related SOCs) in co-infected subjects treated with etravirine (11.1%) compared to not co-infected subjects (4.5%). This trend was not clear in the placebo group (5.9% vs. 5.2%).

A consolidated analysis of Week 48 safety data showed that Grade 3 or 4 elevations in ALT were observed in 11.1% of co-infected subjects treated with etravirine compared to 7.5% of co-infected subjects in the placebo group. For AST, these values were 9.7% and 6.0%, respectively. The incidence of hepatic events tended to be higher in co-infected subjects treated with etravirine compared to co-infected subjects in the placebo group. Therefore, hepatic monitoring for co-infected patients treated with etravirine is included in the Risk Management Plan.

Pancreatic events

Pancreatitis was reported in 4 (0.7%) subjects in the etravirine group and in 2 (0.3%) subjects in the placebo group.

Pancreatitis should be monitored.

Cardiac events

Coronary artery events and myocardial infarction in particular, were closely followed in the DUET trials. At 24 weeks, cardiac events were reported infrequently in both treatment groups (5.8% in etravirine group vs 5.3% in placebo group). Three subjects in the etravirine group and 1 subject in the placebo group died due to a cardiac event. Grade 3 or 4 cardiac events were reported in 1.5% and 1.8% of the subjects in the etravirine and placebo group. Cardiac events were reported as an SAE in 2.0% and 1.3% in the etravirine and placebo group. Permanent discontinuation of the investigational medication due to a cardiac event was reported in 0.5% and 0.3% of the subjects in the etravirine and placebo group. Three subjects in the etravirine group and 1 subject in the placebo group died due to a cardiac event. There were no consistent or clinically relevant changes over time in vital signs or ECG parameters, including QTc.

During the assessment procedure, additional 48-week data on cardiac events from the DUET studies were provided. Cardiac events were reported in 7.0% of subjects in the etravirine group and in 7.3% of subjects in the placebo group. Grade 3 or 4 cardiac events were reported in 2.0% and 2.3% of the subjects in the etravirine and placebo group. Cardiac events were reported as an SAE in 2.8% and 2.0% of subjects in the etravirine and placebo group. Permanent discontinuation of the investigational medication due to a cardiac event was reported in 0.7% and 0.3% of the subjects in the etravirine and placebo group. Three subjects in the etravirine group and 1 subject in the placebo group died due to a cardiac event. None of these deaths was considered related to the investigational medication.

A difference was observed between etravirine and placebo in terms of frequency of occurrence of coronary events in the Week 48 DUET analysis: Adverse events related to myocardial infarctions/ischemia were reported in 8 subjects (1.3%) in the etravirine group and 5 subjects (0.8%) in the placebo group. Incidence of coronary artery disorders: 11 subjects (1.8%) in the etravirine group and 8 subjects (1.3%) in the placebo group.

Most of the ECG findings were considered minor and not clinically relevant. No analysis could be made because of missing data such as medical history or symptomatology.

The signal of coronary events observed during the development of etravirine is included as potential risk in the Risk Management Plan.

Coagulation parameters

Coagulation disturbances were documented in preclinical studies in rodents (mediated via a Vitamin K pathway). In the pooled 48-week safety data provided during the assessment, etravirine was not associated with an increased risk of coagulation disturbances. Taken together all available clinical data it is concluded that etravirine is not associated with an increased risk of coagulation disturbances in humans.

Deaths

A total of 51 subjects died during the entire etravirine clinical development program. Of these 51 subjects, 10 subjects died during the screening phase before the start of investigational treatment. In the DUET trials, 8 subjects died during the screening period, before randomization. All 8 subjects died because of an AE in the SOC infections and infestations, i.e., pneumonia (6 subjects), sepsis (1 subject), and pneumococcal meningitis (1 subject).

In the DUET trials, 23 subjects died due to AEs starting during the treatment period: 8 (1.3%) subjects in the etravirine group and 15 (2.5%) subjects in the placebo group. Three subjects of the etravirine group experienced fatal SAEs considered doubtfully related to etravirine :

- renal impairment and respiratory tract infection in one subject,
- *Mycobacterium avium* complex infection in one subject and,

– myocardial infarction in another subject.

- Laboratory findings

The most common treatment-emergent grade 3 or 4 laboratory abnormalities in the etravirine group were increases in pancreatic amylase (7.5% vs. 7.9% in the placebo group), triglycerides (7.0% vs. 4.3%), total cholesterol (5.8% vs. 4.1%) and LDL cholesterol (5.2% vs. 5.4%). A trend for a higher incidence of grade 3 or 4 abnormalities in triglycerides and total cholesterol was seen in the etravirine group, while there was no substantial difference in the incidence of grade 3 or 4 abnormalities in LDL cholesterol and pancreatic amylase between the etravirine group and placebo group.

Increased ALT and AST (grade 3 and 4) each led to permanent treatment discontinuation of 2 subjects (0.3%) in the etravirine group (none in the placebo group). No other laboratory abnormalities led to permanent discontinuation in more than 1 subject.

- Safety in special populations

The safety profile of etravirine in children and adolescents has not been studied.

The safety profile of etravirine in adults above 65 years old has not been well established. In the DUET trials, 6 subjects aged ≥65 years and 53 subjects aged 56-64 years received etravirine.

- Discontinuation due to adverse events

In the DUET studies the most common ADR leading to discontinuation was rash (any type) (2.0% in the etravirine group vs 0% in the placebo group).

- Post marketing experience

No post-marketing experience is available yet.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 21 Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified Risks		
Rash	**Routine pharmacovigilance** Including close monitoring and appropriate documentation of spontaneously reported cases of severe skin reactions, through enhanced and standardised follow-up activities. Including a discussion on rash in each PSUR, with particular	Listed in the Special warnings and precautions section of the SmPC (section 4.4), including advice for caution. Rash, Erythema multiforme and Stevens-Johnson syndrome are listed as an ADR in Section 4.8.

	attention to patients with a history of rash to NNRTIs. The Company will also participate in the ongoing European Regiscar study with the aim of further monitoring and characterising severe skin reactions in patients receiving INTELENCE.	
Important Potential Risks		
Hepatotoxicity	**Routine pharmacovigilance** Monitoring of hepatic events in co-infected subjects in ongoing and planned studies and routine PV monitoring.	Hepatic steathosis, increased ALT/AST, cytolytic hepatitis, hepatic steatosis, hepatitis and hepatomegaly are listed as ADRs in Section 4.8.
Pancreatitis	**Routine pharmacovigilance**	Pancreatitis, increase in amylase and lipase are listed as an ADR in Section 4.8.
Hyperlipidaemia	**Routine pharmacovigilance** **Monitoring long-term safety through HAART Oversight Committee.**	Hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia and dyslipidaemia are listed as ADRs in Section 4.8.
Coronary artery disorders	**Routine pharmacovigilance** **Monitoring long-term safety through HAART Oversight Committee.**	Myocardial infarction and angina pectoris are listed as an ADR in Section 4.8.
Development of drug resistance	**Routine pharmacovigilance** Collection of additional data from ongoing and planned clinical trials: (TMC125-C206, TMC125-C216, TMC125-C217 and TMC125-C237).	Emergence of resistance (mutations) and effects of baseline resistance on virologic response are listed in Section 5.1.
Important Missing Information		
Use in children and adolescents	Monitor safety data from ongoing and planned clinical trials: TMC125-C126, C213 and C234	Section 4.2. indicates that insufficient data on safety and efficacy in children and adolescents are available.
Use in pregnancy	**Routine Pharmacovigilance** In-utero exposure is captured via the SAE reporting process and will be reported in the PSURs. Post authorisation in-utero exposure will also be captured within the US Antiretroviral Pregnancy Registry. The Registry will provide a 6-monthly report which will be discussed in the PSURs.	Listed in Section 4.2. Recommendation of use in pregnancy in SmPC (Section 4.6). Warning of use during lactation is listed in SmPC (Section 4.6).
Use in elderly	**Routine pharmacovigilance**	Listed in Section 4.2. Listed in the Special warnings and precautions section of the SmPC (section 4.4).

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical aspects of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the benefit risk balance of the product.

Non-clinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that etravirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor with high antiviral potency against wildtype and non-nucleoside reverse transcriptase inhibitor-resistant HIV-1. Being a flexible molecule it is able to bind in the non-nucleoside reverse transcriptase inhibitor binding pocket of the HIV-1 reverse transcriptase in multiple conformations. No inhibitions of the human DNA polymerases alpha, beta, and gamma were observed, and no antiviral activity against a variety of other viruses. The secondary pharmacodynamics and safety pharmacology program revealed that etravirine had inhibitory effects on nicotinergic nerve-smooth muscle function at micromolar concentrations, though it was devoid of muscarinic effects. No other relevant effects of etravirine on *in vitro* and *in vivo* cardiovascular electrophysiological parameters respiratory parameters, neurobehaviour, motor activity or any other body functions, were found for the tested experimental conditions.

From a pharmacokinetic point of view, comparison of exposures achieved in animal species (after repeated administration) with data obtained in HIV-infected patients (treated with the therapeutic dose) showed that the highest C_{max} ratio (animal/human) was around 3 in mice and female rats, and 2 in male rats and 13 in dogs. The highest AUC ratio (animal/human) was 8 in dogs and around 1 in mice, female rats and rabbits but less than 1 in male rats. In general, the ratio was influenced by the physical form of the active substance and the duration of administration due to enzymatic auto-induction, which reduced exposure upon repeated administration in animals.

Overall the toxicology studies revealed that the key target organs in rats were the liver, the thyroid and the coagulation system. Changes in the liver and thyroid were considered adaptive or rodent-specific. Dosing etravirine HBr up to 12 months was not associated with target organ toxicity in the dog. Dosing spray-dried etravirine further increased exposure in the dog and this resulted in hepatic and gall bladder changes in a 1- and 6-month study. The main target organs in the mouse after gavage dosing were the liver and the coagulation system and the heart as a secondary target to changes in coagulation (only after dietary dosing). All genotoxicity tests have not shown any genotoxic potential of etravirine. The evaluation of long-term carcinogenicity studies is still on-going, and data will be provided post approval. No relevant effects were observed in reproduction toxicity studies. Etravirine impacts the vitamin K pathway although the exact mechanism is not known; clinical data does however not suggest that etravirine is affecting the coagulation parameters in patients.

In conclusion, the nonclinical programme is considered adequate to support the use of etravirine in the proposed therapeutic indication with specific aspects being sufficiently addressed in the Summary of Product Characteristics as well as the Risk Management Plan.

Efficacy

Etravirine is a representative of the class of non-nucleoside reverse transcriptase inhibitors (NNRTI). The drug-drug interaction profile of etravirine has been extensively studied. Given that the compound has inducer (CYP3A4) and inhibitor (CYP2C9, CYP2C19, PgP) effects, the sense of the interaction is difficult to predict.

Due to significant limitations of the efficacy demonstration provided by the phase II studies, the dose selection (200 mg b.i.d. with the commercial F060 formulation) is not considered convincingly substantiated. However, the adequacy of the dose is ultimately appreciated with the results of the

Phase III studies.

These two Phase III studies, DUET-1 and DUET-2, have shown that etravirine is able to provide an adequate virologic response in heavily treatment-experienced patients with viral strains harbouring NNRTI resistance. In the "not *de novo* ENF" main subgroup, etravirine is shown to be statistically superior to the placebo arm at Week 24 ($p<0.0001$). Several aspects of the study design deserve to be underlined:

- In both treatment arms patients were receiving darunavir/ritonavir, which is a rather unusual scenario since one of the components of the OBT is pre-defined.
- The existence of a statistical interaction between enfuvirtide "naïve use" and etravirine was anticipated. The results showed that any significant benefit of etravirine was not observed when enfuvirtide was used *de novo*.
- The studies were powered to detect a 20% difference in term of percentage of responders (<50 copies/ml) over the placebo arm. This design is quite challenging for the efficacy demonstration of etravirine, insofar as its added contribution is to be shown in combination to two potent antiretroviral drugs (i.e. darunavir/ritonavir and enfuvirtide)
- To allow for the assessment of the durability of the virologic response and of the emergence of resistance as well as for the assessment of the long term safety, the study duration has been extended from 48 weeks to 96 weeks.

As regards the extrapolation of the data derived from the DUET studies to the combined use of etravirine with other boosted protease inhibitors than darunavir/ritonavir, it is important that, based on the available pharmacokinetic interactions, darunavir/ritonavir has been shown to significantly decrease the etravirine exposure (approx 40%) and C_{min} (approx 50%). Such an interaction is more noticeable with tipranavir/ritonavir but much less marked with other boosted protease inhibitors. Therefore, at the exception of the combined use of tipranavir/ritonavir, the extrapolation of the DUET studies to the combined use of other boosted protease inhibitors appears reasonable. Nevertheless, to provide reassurance of the combined use of etravirine with boosted protease inhibitors other than darunavir/ritonavir, the CHMP requested the conduct of a dedicated confirmatory study post approval as part of the specific obligations of the conditional marketing authorisation.

The available resistance data showed that the presence of the mutation K103N solely did not appear to affect the response in the etravirine group. However, certain analyses are requested to further substantiate whether K103N in combination with other NNRTI mutations influences the virologic response to etravirine. This is critical in the perspective of the use of etravirine in NNRTIs experienced patients, given that most patients will be expected to have viral strains harbouring the K103N NNRTI-signature mutation.

Moreover, for a proper use of etravirine, it is important to take into account that its virologic response will be lost if 3 or more among the 13 identified resistance associated mutations are present at baseline (i.e the so called etravirine RAMs: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S). Although improved as compared to that of existing NNRTIs, the genetic barrier of etravirine is limited. Its use will need to be adequately "protected" by active components within the antiretroviral combination therapy.

Safety

The use of etravirine is associated with rash as an identified risk, which is not unexpected for this class of antiretroviral compounds. In the Phase III trials rash (any type), combining all rash-related terms reported during treatment and/or follow-up, was reported in 17.0% of subjects in the etravirine group compared to 9.4% in the placebo group which is significantly higher. The scarcity of the safety data in patients with history of cutaneous reaction with NNRTIs [<10% (n=48)] mandates caution in the future use of etravirine in such patients. Attention of prescribers is being alerted on this issue by a specific warning in the SmPC.

The most common treatment-emergent grade 3 or 4 laboratory abnormalities in the etravirine group were increases in pancreatic amylase (7.5% vs 7.9% in the placebo group), triglycerides (7.0%vs

4.3%), total cholesterol (5.8% vs 4.1%) and LDL cholesterol (5.2% vs 5.4%). These laboratory findings should be monitored on a long-term because of the cardiovascular risk, further analysis should be provided.

Pancreatic events should be monitored.

Overall, the pooled analysis of Week 48 safety data from the DUET studies is reassuring as regards the long term safety of the compound, the 96 weeks data are awaited to give further reassurance.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A user consultation for the proposed package leaflet has been performed in HIV infected patients. No weaknesses of the package leaflet were identified. Overall, the test was considered acceptable.

Risk-benefit assessment

Benefits

The benefit of etravirine is demonstrated by the efficacy results in the two pivotal studies, DUET 1 and DUET 2, in which etravirine adequately demonstrated virologic response in a difficult to treat patient population. The combinations investigated in these studies were challenging for etravirine and will need to be further explored within the pooled 48 weeks efficacy analysis.

Overall, up to now, the poor genetic barrier of NNRTIs (a single mutation (K103N) could induce a high level of resistance) and cross resistance between NNRTIs, did not allow the rescue of a patient failing an NNRTI containing regimen by another NNRTI. Given its pharmacodynamic properties (improved genetic barrier and difference in the resistance pattern of the compound as compared to existing NNRTIs) etravirine could be explored in patients failing NNRTI therapy. Beyond the pharmacodynamic claims, the applicant has provided an acceptable demonstration of the benefit of the compound in such context, patients being selected on the very basis of NNRTIs resistance.

The use of etravirine with boosted protease inhibitors other than darunavir/ritonavir is currently based on extrapolation. The applicant committed to perform an additional confirmatory study aimed at providing further reassurance on the extrapolation of the DUET clinical results to the combined use of etravirine with boosted protease inhibitors other than darunavir/ritonavir. The protocol of this planned study will need to be agreed with the CHMP before the study starts.

Risks

Etravirine shares with existing NNRTIs the class effect of cutaneous skin reaction. The scarcity of the safety data in patients with history of rash to NNRTIs mandate caution in the use of etravirine in such patients. Contrarily to efavirenz (another NNRTI) no psychiatric adverse events have been observed so far in phase III studies.

Other concerns have been identified that will need to be monitored through the risk management programme, notably hepatotoxicity, pancreatitis, hyperlipidaemia, and coronary artery disorders. Development of resistance is also part of the Risk Management Plan.

Balance

Based on the available data, and in particular the phase III studies, the CHMP considers that etravirine has demonstrated to be able to provide an adequate virologic response in antiretroviral experienced patients with viral strains harbouring NNRTI resistance, and that these benefits outweigh the risks identified or anticipated with the use of etravirine.

The CHMP considered the criteria for a conditional marketing authorisation according to Article 14(7) of Regulation (EC) No 726/2004 in conjunction with Commission Regulation (EC) 507/2006. Based on the assessment the CHMP concluded that the application meets the criteria for conditional marketing authorisation, for the following reasons:

- Etravirine is indicated for the treatment of HIV-1 infection, which is a life threatening condition, therefore the application, being made under Article 3(1) of Regulation (EC) 726/2004, is in the scope of conditional marketing authorisation according to the Article 2(1) of Regulation (EC) 507/2006.
- Based on the available data and particularly the 24-week data from the two pivotal trials (DUET-1 and DUET-2) the risk-benefit balance is considered positive as these studies have shown that etravirine is able to provide an adequate virologic response in antiretroviral experienced patients with viral strains harbouring NNRTI resistance. Additional clinical data is needed to further substantiate the durability of virologic response and the use in combination with protease inhibitors other than darunavir/ritonavir, respectively. It is considered that the applicant will be in a position to provide these data so that eventually the data package will become comprehensive. Although not representing a new pharmacological class, etravirine does answer an unmet medical need in antiretroviral experienced HIV-infected patients with limited therapeutic options, insofar as it represents an additional tool for controlling the viral replication in patients harbouring multi-resistant strains. The pharmacological properties of etravirine make it an important antiretroviral treatment option in addition to recently approved compounds representing new classes of antiretroviral medicinal products. From a public health perspective the benefit of allowing etravirine to be marketed without undue delay may outweigh the risks inherent in the fact that additional data are still required. The requirements for a conditional marketing authorisation according to the Article 4(1) of Regulation (EC) 507/2006 are therefore met.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns;
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of INTELENCE in the therapeutic indication

> "INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients (see sections 4.4, 4.5 and 5.1).
>
> This indication is based on week 24 analyses from 2 randomised, double-blind, placebo-controlled Phase III trials in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, where INTELENCE was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir (see section 5.1)."

was favourable and therefore recommended the granting of the conditional marketing authorisation.