

SCIENTIFIC DISCUSSION

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

1. Introduction

Over the last few years, a decrease in the morbidity associated with AIDS and an increase in survival times in association with sustained suppression of viral replication has been achieved in North America and Europe, primarily because of the use of highly active antiretroviral therapy (HAART). Current options for the treatment of Human Immunodeficiency Virus (HIV-1) consist of four different mechanistic classes of compounds: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and fusion inhibitors. The choice of the combination regimens depends on the status of the patient, particularly in terms of plasma viral load (HIV RNA), CD4 cell counts, previous treatment(s), prior relapse and intolerance to treatment.

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

Telzir contains fosamprenavir, which is the prodrug of amprenavir, a non-peptide competitive inhibitor of the HIV protease enzyme. Fosamprenavir has no or little antiviral activity *per se*, and requires in-vivo metabolism to release the active moiety amprenavir. A medicinal product containing amprenavir has already been granted a marketing authorisation for the treatment of HIV infection, however its inherent low solubility has resulted in a commercial formulation requiring taking a large number of capsules per day.

Telzir has therefore been developed not only to optimise the use of amprenavir, by further reducing the pill burden but also to optimise/complete the clinical development of this compound in HIV infected naïve and pretreated patients. Telzir is available both as film-coated tablets containing 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir) and oral suspension containing 50 mg/ml fosamprenavir as fosamprenavir calcium (equivalent to approximately 43 mg/ml amprenavir).

The approved indication is: "Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products. In moderately antiretroviral experienced patients, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir. In heavily pretreated patients the use of Telzir in combination with low dose ritonavir has not been sufficiently studied. In protease inhibitor (PI) experienced patients the choice of Telzir should be based on individual viral resistance testing and treatment history."

2. Chemical, pharmaceutical and biological aspects

Telzir is available in two pharmaceutical forms i.e. film-coated tablet and oral suspension.

Film-coated tablets

Telzir film-coated tablet contains 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir).

The other ingredients include:

- Tablet core: microcrystalline cellulose, croscarmellose sodium, povidone K30, magnesium stearate, colloidal anhydrous silica,

- Tablet film coating: hypromellose, titanium dioxide, glycerol triacetate and iron oxide red.

The tablets are packed in HPDE bottle with child resistant closure.

Oral suspension

Telzir oral suspension contains 50 mg/ml of fosamprenavir as fosamprenavir calcium (equivalent to approximately 43 mg/ml of amprenavir).

The other ingredients include propylene glycol, hypromellose, sucralose, methyl parahydroxybenzoate, propyl parahydroxybenzoate, polysorbate 80, calcium chloride dihydrate, artificial grape bubblegum flavour, natural peppermint flavour and purified water.

The oral suspension is presented in a multidose HPDE bottle with child resistant polypropylene closures. A 10 ml dosing syringe and a syringe adaptor are provided.

Drug Substance

Fosamprenavir is the phosphate ester prodrug of amprenavir. A medicinal product containing amprenavir has already been approved via the centralised procedure. Fosamprenavir is present in the finished products as the calcium salt.

The active substance is a white to cream coloured solid. It is very slightly soluble in water and its water solubility is pH dependant (maximum solubility at pH 3 to 4).

Structure elucidation has been conducted by standard methods (elemental analysis, NMR, MS, IR and single crystal X-ray crystallography). Fosamprenavir contains 3 chiral centres, but it is synthesised as the single enantiomer *3S*, *1S*, *2R*. Experimental data have shown that the inversion of the chiral centres during the synthesis and storage is very unlikely.

Only one crystalline form has been identified, produced and used in non-clinical/clinical studies. It contains approximately 5 molecules of water, but it cannot be considered as a strict pentahydrate.

- **Manufacture**

The synthesis of fosamprenavir is similar to the one authorised for amprenavir with the exception of the last steps: phosphate esterification, final isolation of calcium salt and milling.

One of the starting materials uses stearylamine, a bovine tallow derived material, as an anticaking agent in its preparation. The potential TSE risk associated with stearylamine has been satisfactorily addressed.

Satisfactory specifications and associated methods have been provided for the starting materials, intermediate, reagents and solvents.

- **Specification**

The active substance specification include test for appearance, identity (IR and calcium flame test), assay (HPLC, NLT 98.0 % - NMT 102.0 %), water content (PhEur), impurity content (HPLC), residual solvents (GC), palladium content (skip testing) and particle size.

The formation of the desired enantiomer of fosamprenavir is ensured through the use of key starting materials of high stereochemical purity and the route of synthesis. A chiral identity test will be developed on an ongoing basis. Therefore, the omission of a chiral assay for the claimed enantiomer and a chiral determination of the opposite enantiomer in the specifications have been supported in this particular case.

Only one quality of drug substance in terms of particle size is used for the tablet and oral suspension, with an additional specification for the latter. This is in line with the need for resuspendibility of the suspension (see oral suspension pharmaceutical development).

Specification limits have been adequately justified by analytical, stability and toxicity data. The analytical methods used in routine controls have been suitably described and validated.

Batch analysis data provided for 6 recent batches manufactured at the commercial synthesis site confirm satisfactory compliance and uniformity with the proposed specification.

- **Stability**

Under intermediate conditions (30°C/60 %RH - intended packaging), 24-month stability data have been provided for 3 pilot scale batches and 12-month for 3 industrial scale batches. Under accelerated conditions (40°C/75 %RH - intended packaging) 6-month data have been provided. A photostability study has been performed and indicates that fosamprenavir is not light sensitive. A retest period of 3 years with precaution for storage of “Store up to 30°C” has been adequately justified and is supported by the presented data when the substance is stored in metal, plastic or fibreboard containers lined with anti-static low-density polyethylene bags and sealed with plastic ties.

Drug Product

Film-coated tablets

- **Pharmaceutical Development**

Due to the low aqueous solubility of amprenavir and the need for a high ratio of excipients/amprenavir in the formulation, amprenavir capsules have been formulated as low-strength large soft capsules requiring administration of several capsules daily. In order to ensure a lower pill burden and keep the tablet size to a minimum in the case of fosamprenavir, a formulation with a high drug load and low level of excipients has been developed.

The excipients have been selected based on their compatibility with the drug substance by means of statistically designed excipient interaction studies on powder mixes. They are all of European Pharmacopoeia quality except the film-coating, which is satisfactorily controlled according to a different standard. An appropriate level of each excipient has been established through a multifactorial formulation design.

Due to a combination of high drug content and small particle size of the drug substance causing poor blend flow properties, direct compression was not feasible and a classical high shear wet granulation process has been developed.

The suitability of the primary packaging selected i.e. HPDE bottle with child resistant closure has been demonstrated by stability studies. It is in compliance with European regulation on plastic materials and articles intended to come into contact with foodstuffs. Regarding the TSE risk, stearylamine is the only component of ruminant origin used in the manufacture of Telzir (see drug substance).

The main phase III clinical trials were performed using 3 “variants” of the 700 mg film-coated tablets A, B and C, corresponding to different scale up of the drug substance/drug product and particle size of the drug substance. In the first instance, bioequivalence was not established between these 3 variants and the reasons for it seem not to be clearly identified. However, bioequivalence studies APV10021 and APV10029 demonstrated that both scale-up of the drug substance and of the drug product, and the particle size of the drug substance have no impact *in vivo* and thus are of no clinical relevance (see Section 3.4 Clinical aspects – Pharmacokinetics)

In addition, an appropriate drug substance particle size specification has been established (see drug substance) and only one quality of tablets i.e. variant C will be commercialised, thus ensuring a drug product of consistent quality.

- **Manufacture of the product**

The manufacturing process involves the following conventional operations: high shear wet granulation, drying, milling, blending, tablet compression, film-coating and packaging. Two granulation batches may be combined prior to addition of the extra granular excipients to form a compression/film coating batch.

Satisfactory validation data on production-scale batches have been provided. Together with process development data, they show that the manufacturing process is robust and well controlled. The hydration state and solid-state form of the drug substance are not affected during the manufacturing process involving heating of the product.

- **Product specification**

The product specification includes tests controlled by validated methods for appearance, identity (IR), identification of colourants, assay (HPLC), impurity content (HPLC), dissolution, uniformity of mass (PhEur) and microbial limit (PhEur – non routine test).

Water activity and microbial limit tests have confirmed that the water associated with fosamprenavir does not promote microbial growth in the drug substance and product, and thus that a routine microbial limit test is not necessary.

Batch analysis data provided for 6 batches comply with the specifications and indicate consistent and reproducible manufacture.

- **Stability of the product**

Under long-term conditions (30°C/60 % RH – intended packaging), 30-month data have been provided for 2 pilot scale batches and 24-month for 1 pilot scale batch. Accelerated data (40°C/75 % RH - intended packaging) have been provided up to 6 months.

The data provided support the proposed shelf life and storage conditions as defined in the Summary of Product Characteristics.

Oral suspension

- **Pharmaceutical Development**

This oral formulation has been mainly developed for patients, who have difficulties in swallowing tablets.

The particle size, distribution of the drug substance, has been shown to impact on the suspension properties, especially redispersibility. This has been taken into account in fosamprenavir specification (see drug substance).

All the excipients have been selected based on their compatibility with the drug substance in order to ensure minimal agglomeration and easy redispersibility of the suspension. A 1% w/w level of propylene glycol was chosen in order to ensure solubility of the preservatives without affecting the redispersibility of the formulation. The pH selected is satisfactory for the physical properties of the suspension. In addition, it maintains the antimicrobial efficacy of the preservatives, which has been demonstrated according to PhEur at release and during storage. Taste masking of fosamprenavir is achieved by using sucralose and by inclusion of two flavours. Patient acceptability of the taste and palatability of the oral suspension has been confirmed. All the excipients are of PhEur quality except sucralose and flavours, which are adequately controlled according to different standards. Regarding the TSE risk, stearylamine is the only component of ruminant origin used in the manufacture of Telzir (see drug substance).

Satisfactory specifications have been provided for the HDPE bottle and the child-resistant polypropylene closure. The compatibility of suspension with the primary packaging has been satisfactorily demonstrated. The oral syringe is CE marked and has been approved for its intended use. The accuracy and reproducibility of the dose delivered by this medical device has been satisfactorily demonstrated.

Satisfactory minimum shaking time to ensure redispersibility prior to extracting the first dose and subsequent doses have been determined based on studies simulating patient-use conditions at low and high doses. No significant differences in drug substance content were observed at any of the dosing intervals, dose regimes and shaking times

- **Manufacture of the Product**

Methyl and propyl parahydroxybenzoate are solubilised in propylene glycol before mixing with the bulk hypromellose dispersion, and drug substance dispersion along with the other excipients in a sequence that ensures optimal stability of the product.

Validation data on commercial scale batches manufactured by the proposed commercial site have been provided. A maximum hold time of 7 days for the bulk suspension prior to filling has been set based on satisfactory physicochemical and microbiological validation.

- **Product specification**

The product specification includes tests controlled by validated methods for appearance, identity (IR), identification of preservatives (HPLC), assay (HPLC), preservative content (HPLC), impurity content (HPLC), dissolution, uniformity of content, pH (PhEur), deliverable volume, redispersibility (HPLC) and microbial limit (PhEur).

Batch analysis data provided for 3 production batches comply with the specifications and indicate consistent and reproducible manufacture.

- **Stability of the product**

24-month long-term stability data (30°C/60 % RH - proposed commercial packaging) on 1 pilot-scale and 18-month data (25°C/40 % RH and 30°C/60 % RH- proposed commercial packaging horizontal position) on 3 production-scale batches have been provided. Accelerated data (40°C/75 % RH) have been provided up to 6 months.

Photostability studies have shown that the finished product is non-light sensitive. A satisfactory in-use stability study has been performed. The data provided support the proposed shelf life, in-use shelf life and storage as defined in the Summary of Product Characteristics.

- **Bioequivalence between pharmaceutical forms**

The oral suspension under fasting conditions delivered an equivalent plasma amprenavir (APV) AUC_∞ and a 14% higher C_{max} relative to the tablet formulation (means ratio: 1.145, 90% CI: 1.011-1.297) and therefore the suspension should be administered without food at the same dose as the film-coated tablets. The slight difference in C_{max} is not considered to be relevant in the clinical use of these products.

3. Toxicopharmacological aspects

Fosamprenavir has little or no antiviral activity by itself and requires in-vivo metabolism to release the active moiety of amprenavir. Amprenavir is the non-peptidic competitive inhibitor of the HIV-protease. It blocks the ability of the viral protease to process viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Early in the development, the disodium salt of fosamprenavir was used. However due to its superior pharmaceutical properties, the calcium salt was later used. This is the proposed form for commercial use.

In addition to the non-clinical studies performed with fosamprenavir, data previously obtained with amprenavir, which are relevant for this application, have been submitted.

All definitive toxicokinetics and toxicological studies were claimed to be performed in compliance with Good Laboratory Practices.

Pharmacology

- **Primary pharmacodynamics**

As the antiviral activity of amprenavir has previously been established, new virological and pharmacological studies were performed to demonstrate the lack of intrinsic anti-HIV activity of fosamprenavir calcium salt and its conversion to amprenavir in the small intestine. The general pharmacological activity and safety of fosamprenavir has also been investigated in a range of in-vitro and in-vivo studies. Some additional studies have been carried out with amprenavir to complete its general pharmacological profile.

Overall, amprenavir is a potent non-peptide inhibitor of HIV-1 and HIV-2 protease with little effect on cellular aspartic protease. Against HIV-1 (HXB2) the mean inhibitor concentration (IC₅₀) was 0.085 µM. Anti-HIV-1 activity was demonstrated in both acutely and in chronically infected cells.

Fosamprenavir showed no significant inhibition of HIV protease with a constant inhibition (K_i) value of 20 nM compared to 0.04 for amprenavir. In MT4 cells infected with HIV-1 strain IIIB, fosamprenavir showed negligible antiviral activity with IC_{50} of 1250 ± 381 nM for fosamprenavir versus 88 ± 10 nM for amprenavir. As the efficacy of fosamprenavir accounted from the antiviral activity of amprenavir, which is present as an impurity of the prodrug, no further experiments with other HIV-1 and HIV-2 strains were deemed necessary.

Fosamprenavir had minimal cytotoxic effects on human bone marrow progenitor cells or immortalised T-cells lines.

Fosamprenavir and amprenavir had minimal effects on ligand binding to over 60 receptors, transporters or enzymes tested at plasma concentration up to 10 μ M, equivalent to approximately 5 μ g/ml amprenavir or 6 μ g/ml free acid form. Therefore neither compound is expected to cause secondary pharmacological effects through interaction at these sites.

In vitro amprenavir had no effects on lipid metabolism in C3HIOTI/2 cells, in Hep G2 cells and rat hepatocytes. In addition amprenavir had minimal effects *in vivo* on the metabolic parameters tested in two strains of mice after subcutaneous implementation of continuous release pellets containing 60 mg amprenavir for 2 weeks. These included insulin resistance index, markers of fat metabolism and markers of liver, kidney and heart/muscle function.

- Safety pharmacology

Fosamprenavir (sodium salt) did not cause any treatment-related overt effects on the central and peripheral nervous systems, the cardiovascular and respiratory systems in rats and dogs with doses up to 2000 mg/kg (1493 mg/kg amprenavir equivalents).

In vitro, fosamprenavir (calcium salt) showed no clinically relevant effects on the action potential duration of isolated dog Purkinje fibres. Studies with amprenavir indicated a shortening of the repolarisation phase of the cardiac action potential, but these results were not observed *in vivo* in the dog toxicology studies. Neither compound had any effect on the hERG current *in vitro*. These results suggest that QTc prolongation would not be seen in humans following administration of fosamprenavir (calcium salt).

- Pharmacodynamic drug interactions

Specific studies investigating pharmacological drug interactions have not been performed however the results of the in-vitro receptor screen study indicate that potential interactions are unlikely. Moreover potential interactions with other medicinal products have been evaluated in clinical trials.

Pharmacokinetics

The pharmacokinetics profile of fosamprenavir has been defined in mice, rats, rabbits and beagle dogs. Studies aimed to describe the disposition and metabolism of both amprenavir and fosamprenavir (free ester) following oral administration of the calcium salt or in some studies the disodium salt. Toxicokinetics data derive from repeated dose toxicity studies.

Fosamprenavir (free ester) and amprenavir were measured in biological samples using adequate methods of assays.

- Absorption- Bioavailability

In-vitro and in-vivo data were submitted to corroborate the hypothesis that fosamprenavir is primarily hydrolysed to amprenavir in the intestinal epithelia by an intestinal alkaline phosphatase and not largely absorbed. These data further support the hypothesis that the safety and efficacy profile of fosamprenavir would be similar to amprenavir. An in-vitro study demonstrated that ritonavir did not inhibit the activity of a human intestinal alkaline phosphatase. The administration of low dose of ritonavir with fosamprenavir calcium salt is therefore not expected to significantly alter the conversion of fosamprenavir to amprenavir.

Following a single oral administration of fosamprenavir (calcium salt), amprenavir was rapidly absorbed in mice, rats and dogs with T_{max} values of approximately 1 hour or less.

The oral bioavailability of fosamprenavir (calcium salt) is very low as the hydrolysis to amprenavir is extensive. The absolute oral bioavailability is unknown but estimation has been made. The exposure to amprenavir following fosamprenavir (calcium salt) administration was approximately 60 or 80 % that following oral amprenavir administration in rats or dogs, respectively. Therefore, as the bioavailability of amprenavir following oral amprenavir administration in rats and dogs is 40 and 100 %, the estimated oral bioavailability of amprenavir following oral administration of fosamprenavir (calcium salt) is approximately 25 % in rats and 80 % in dogs, respectively.

On repeat oral administration of fosamprenavir (disodium or calcium salt) to mice, rats, rabbit or dogs, plasma concentrations of fosamprenavir (free ester) were highly variable; no consistent pattern of decrease or increase in systemic exposure to fosamprenavir (free ester) was observed over time. Exposure ratios of fosamprenavir (free ester) to amprenavir were generally < 3 % in mice, < 2 % in rats and < 1 % in dogs, indicating extensive conversion during absorption. This ratio was higher in rabbit and increased in all species at the highest doses, showing a saturation of the conversion.

Systemic exposure to amprenavir increased in a generally dose-related, but not dose-proportional manner. In rats and mice, exposure decreased on repeat dosing suggesting autoinduction whereas in dogs and rabbits exposure increased.

There was no effect of pregnancy on exposure to either amprenavir or fosamprenavir (free ester) in rats. However in pregnant rabbits exposure to amprenavir was dose-related, and increased in a greater than dose-proportional manner.

Plasma concentrations of amprenavir and fosamprenavir (free ester) were higher after oral administration in neonatal/juvenile rats compared to sexually mature rats.

- Distribution

As in-vivo whole body distribution studies had already been carried out with amprenavir and very little fosamprenavir (free ester) is available systemically, these studies were not repeated with the calcium salt. After oral dosing, amprenavir was found primarily in the organs of excretion and metabolism.

Plasma protein binding of fosamprenavir (calcium salt) was approximately 96 % at 0.2 µg/ml. The plasma protein binding of amprenavir was approximately 90%. There was no clinically relevant protein binding interaction between amprenavir and fosamprenavir (free ester), or between amprenavir and its metabolites.

- Metabolism and excretion

The metabolic profiles in the different species and human were qualitatively similar and similar to those seen following administration of amprenavir.

The metabolism in rats involved a di-oxidation on the tetrahydrofuran moiety of the molecule and an additional site of oxidation on the aniline ring portion of the molecule.

Amprenavir was eliminated mainly by hepatobiliary processes and excreted via faeces after administration of calcium salt (> 75 %). Urinary excretion accounted for 5.11, 2.63 or 13 % of the administered dose in mice, rats or dogs, respectively. Excretion of unchanged amprenavir accounted for 11 % in mice, 17 % in rats and 28 % in dogs. Clearance was not measured and estimation of half-life was very variable.

Studies in rats and mice showed that fosamprenavir (calcium salt) induced CYP3A, similar to the findings in rats with amprenavir. This is consistent with the toxicokinetics findings in these species, where amprenavir exposure decreased on repeated dosing. In dogs, no effect on CYP3A was noted following repeated administration of fosamprenavir (calcium salt), although a weak inductive effect on CYP2B was seen.

Contamination of the control samples occurred in many studies during the preclinical development. An investigation suggested that it occurred during sampling or analysis. It was however accepted that the generally low levels of fosamprenavir (free ester) or amprenavir in a small number of control samples did not affect the toxicokinetics evaluation of the studies. Specific measures have nevertheless been implemented in the ongoing carcinogenicity studies to prevent further contamination.

Toxicology

A complete toxicological programme was performed with fosamprenavir since the impurity profile of the calcium salt of the prodrug differs from the one of amprenavir. This is a consequence of different chemical processes employed during the manufacture of the two compounds. In addition, fosamprenavir is not completely hydrolysed to amprenavir, and the prodrug has been detected at low levels (< 0.6 % of amprenavir AUC) systemically in humans following dosing at the proposed therapeutic dose.

This programme included single dose studies (mice and rats), repeated dose studies (rats up to 6 months and dogs up to 9 months), genotoxicity and reproductive and developmental toxicity studies (rats and rabbits). Carcinogenicity studies with fosamprenavir (calcium salt) are ongoing in rats and mice. Other toxicity studies included local tolerance (eye and dermal irritancy in the rabbit) potential sensitisation in the guinea pig, immunotoxicity and impurities. The toxicity in juvenile animals has also been evaluated.

Although the majority of studies were conducted with fosamprenavir as calcium salt, some initial studies used the disodium salt. These initial studies were not repeated as they were superseded by studies using the calcium salt at higher doses and for longer duration. The definitive intravenous single dose studies were all conducted with the disodium salt because of its high solubility in saline.

Although fosamprenavir is to be used with low dose of ritonavir, the combination was not tested in the toxicological studies. This was however considered acceptable in view of the clinical safety profile in patients receiving fosamprenavir (calcium salt) with or without low dose ritonavir and the toxicological profiles for the individual compounds, which do not suggest novel toxicities for the combination.

- **Single dose toxicity**

After oral administration, fosamprenavir either as the disodium salt or calcium salt showed low acute toxicity in mice and rats. The maximum non-lethal dose was > 2000 mg/kg (1493 mg/kg amprenavir equivalents) and > 2986 mg/kg (2000 mg/kg amprenavir equivalent dose) respectively in both species.

After intravenous administration of fosamprenavir as the disodium salt, ataxia and decreased activity were the most noticeable signs of toxicity. The maximum non-lethal dose was 217 mg/kg in mice and female rats (160 mg/kg amprenavir equivalents) and 347 mg/kg (256 mg/kg amprenavir equivalent dose) in male rats.

- **Repeated dose toxicity**

Repeated dose toxicity studies were conducted in rats (2 weeks, 1 and 6 months) and in dogs (2 weeks, 1 and 9 months). The 2 weeks rat and dog studies were conducted with the disodium salt administered orally. In the other studies, the calcium salt was used. Doses ranging from 149 mg/kg (100 mg/kg amprenavir equivalent) to 2240 mg/kg (1500 mg/kg amprenavir equivalent) of fosamprenavir as calcium salt have been tested in rats in the 1 and 6 months studies. Doses ranging from 75 mg/kg (50 mg/kg amprenavir equivalent) to 337 mg/kg (225 mg/kg amprenavir equivalent) of fosamprenavir as calcium salt have been tested in dogs in the 9 months studies.

The major target organ in rats and dogs was the liver. In rats, there were changes in serum clinical chemistry including increased cholesterol, decreased triglycerides, and, in the 6-month study, increased serum activity of AST, ALT, GD and GGT. The activity of AST, ALT and GD was generally higher at the end of the recovery period than it was during the dosing period. Treatment

related increases in absolute (4 to 61 %) and relative (3 to 69 %) liver weights occurred in all studies. Microscopic findings were generally associated with increased liver weights (hepatocyte hypertrophy in the short-term studies, and in long-term studies multinucleated hepatocytes, individual hepatocyte necrosis, increased hepatocyte pigment, increased Kupffer cell pigment and hepatocellular vacuolation). Following the recovery period in rats, the increased liver weights and most of the microscopic liver findings were improving but were not completely recovered to control levels. In dogs, increases (23 to 272 %) in serum alkaline phosphatase concentrations were consistently observed in all the long-term studies. ALT was also increased in the 9-month study only. Increases in liver weights were observed in the 14-day and 4-week studies but not in the 9-month study. The only significant microscopic finding was hepatocellular pigment in the 9-month study. Following the recovery period, the increased liver weights were improving but were not completely recovered to control levels. The microscopic liver findings did not recover. Although the mechanism behind the AST and ALT augmentation at the end of the recovery period is unknown, no liver toxicity is anticipated with the clinical use of fosamprenavir as until now no liver toxicity has been noted after treatment with amprenavir.

In rats, there were consistent haematological changes between the 4-week and 6-month studies including small decreases (1 to 8%) in haematocrit and haemoglobin, and an increase (7 to 25 %) in platelet count. All of these changes appeared to improve during the recovery period, but did not fully recover. In the 6-month study, haematological changes occurred in both male and female rats at doses \geq 478 mg/kg/day (320 mg/kg/day amprenavir equivalents). In the dog, no haematological changes were directly attributed to the administration of fosamprenavir (calcium salt).

In dogs, salivation, vomiting and faecal alterations (soft to liquid faeces) occurred consistently throughout all studies. In the 9-month study, some animals in the highest dose group deteriorated to such an extent that they were euthanised prior to the end of the treatment period, and the two high dose groups were combined and the dose level reduced. These were not considered serious events and were reversible on discontinuation of treatment.

Myocardial changes in rats were observed in some studies however a further analysis of the preclinical data did not reveal statistically significant myocardial effect and there was no effect in the 6-month study. Furthermore, clinical data do not suggest that fosamprenavir has a cardiac effect, however this will be monitored post-authorisation.

Animals were poorly exposed to amprenavir after fosamprenavir (calcium salt) administration: 0.7 to 1.3 fold compared to human exposure at the maximum dosage used in the 6-month study in rats (2240 mg/kg/day equivalent to 1500 mg/kg/day amprenavir), and 1.9 to 3.1 fold in the 9-month study in dogs (337 mg/kg/day equivalent to 225 mg/kg/day amprenavir). However, animals were exposed to a much higher extent to fosamprenavir (calcium salt) as compared to humans (45 to 76 fold the human exposure for rats, and 23 to 68 fold for dogs), thus correctly addressing the toxicity of fosamprenavir. In the rat pivotal 6-month study, the NOAEL found was 149 mg/kg (0.2 to 0.3 fold compared to human exposure for amprenavir; 1.3 to 11 fold compared to human exposure for fosamprenavir (calcium salt)). In the dog pivotal 9-month study, no NOAEL could be established. However, at the lowest dosage used (75 mg/kg) toxicity consisted mainly in hepatocellular pigmentation.

- Genotoxicity in vitro and in vivo

Fosamprenavir was not mutagenic in bacterial or mammalian mutagenicity assays. Fosamprenavir was not clastogenic in the in-vivo micronucleus test in rats (doses up to 2290 mg/kg/day equivalent to 2000 mg/kg/day amprenavir). However, in this test fosamprenavir was administered by the oral route, resulting to exposure in animals close to the one achieved in humans (3.8 fold for fosamprenavir and 1.6 fold for amprenavir). An additional test was performed where rats received 50 mg or 150 mg/kg/day fosamprenavir administered by the intravenous route to maximise exposure to both, using the soluble disodium salt instead of the calcium salt to be used in clinic to get a better animal exposure. The results were negative. In addition, an in-vitro mouse lymphoma assay using the calcium salt was carried out at concentration up to 576.9 μ g/ml confirming the lack of clastogenic potential.

- Carcinogenicity

Carcinogenicity studies with the calcium salt are currently ongoing in rats and mice. In view of the clinical experience with amprenavir, which has not raised any concern in relation to any carcinogenicity potential, the results from the carcinogenicity studies obtained previously with amprenavir, and the therapeutic indication, the CPMP considered that the lack of results should not preclude the granting of the marketing authorisation. Final results will however be submitted as part of the follow-up measures to be fulfilled post-authorisation. Of note, data obtained with amprenavir showed that it caused hepatocellular adenomas in male rats and mice but these findings were considered being part of the continuum of hepatic findings noted in rodents and dogs during the amprenavir non-clinical development programme.

- Reproductive and developmental studies

Fertility studies in rats did not reveal any treatment related adverse effects on reproductive functions. In females, at the high dose (2240 mg/kg/day corresponding to 1498 mg/kg/day amprenavir equivalents), there was a reduction in the weight of gravid uterus (0 to 16 %), probably due to a reduction of the number of ovarian corpora lutea and implantations.

There was no evidence of embryo-foetal toxicity in rats, but at the high dose (2240 mg/kg/day or 1498 mg/kg/day amprenavir equivalents) exposure was lower than the expected human exposure. In rabbits, no overt teratogenicity was noted, but there was a positive trend for foetal soft tissue variations including small or missing intermediate lung lobe in the high dose group although these are likely to be due to maternal toxicity which occurred at low exposure levels. In this study, even at high dose (672.8 or 450 mg/kg/day amprenavir equivalents), exposure to amprenavir was only 0.3 fold that seen in humans administered the maximum proposed clinical dose.

In the pre and postnatal study in rats, fosamprenavir (calcium salt) caused a reduction in pup survival and weight at the high dose (2240 mg/kg/day or 1498 mg/kg/day amprenavir equivalents). Deceased pups often showed diminished milk content of the stomach. There were also signs of delayed physical and functional development. After pups reached maturity and were mated, reproductive effects were observed including a decreased number of implantation sites per litter and a prolongation of gestation. No safety margin could be established due to the limited systemic exposure in animals.

Overall, fosamprenavir should be used during pregnancy, only if the potential benefit to the mother justifies the potential risk to the foetus. In addition, fosamprenavir should not be recommended during lactation.

- Other toxicity studies

Fosamprenavir (calcium salt) did not cause any irritation when applied to the rabbit eye but was classified as a mild irritant to rabbit skin. It showed no sensitising potential in guinea pigs.

A 28 days immunotoxicity study was conducted in rats given orally doses of 0, 300 and 1500 mg/kg/day of fosamprenavir calcium salt. There was no alteration of the primary antibody response to keyhole limpet hemocyanin. Fosamprenavir was not immunotoxic.

Neither amprenavir nor fosamprenavir (calcium salt) at toxicological or therapeutic concentrations interfered with assays for liver function.

All the specified impurities in fosamprenavir calcium salt have been adequately toxicologically quantified.

The toxicity of fosamprenavir (calcium salt) was studied in juvenile rats (starting at 4 days of age) up to 13 weeks, with doses ranging from 100 to 300 mg/kg/day (71 to 213 mg/kg/day amprenavir equivalents). The findings were similar to those seen in adult rats. There was an increase in liver weight, but with less microscopic effects, and an increase in plasma cholesterol and number of platelets. The NOAEL was 175 mg/kg/day. However in contrast to adult rats, there were also some

effects on the kidney (hyaline droplets and increased weight in males). The applicant undertook to further investigate the nature of hyaline droplets and discuss the relevance of these observations to humans.

- Environmental risk assessment

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

4. Clinical aspects

The clinical programme consisted of:

- studies aiming to characterise the pharmacokinetic profile of fosamprenavir following single and multiple administration with or without ritonavir;
- a phase II study (APV 20001) to assess the safety, tolerability, pharmacokinetics and antiviral effect of two doses of fosamprenavir BID compared with amprenavir BID in HIV-1 infected patients;
- Two phase III studies in antiretroviral naïve patients: study APV 30001 where fosamprenavir (1400 mg BID) was non boosted with ritonavir and study APV 30002 where fosamprenavir 1400 mg was boosted with ritonavir low doses (200 mg) once daily;
- One phase III study in antiretroviral experienced patients: study APV30003 using fosamprenavir boosted with low doses of ritonavir. Both once and twice daily regimens were explored (1400 /200 mg OD and 700/100 mg BID of fosamprenavir/ritonavir).

Preliminary data of a phase III study in multi-experienced patients have also been submitted (study 40003). In addition, as fosamprenavir is the prodrug of amprenavir, an antiretroviral agent already authorised, clinical data previously obtained with amprenavir relevant to this application have been provided to support the clinical efficacy and safety.

The applicant claimed that all studies were performed according to Good Clinical Practices.

Pharmacodynamics

- Mechanism of action

As already mentioned in section 3.3 of this document, fosamprenavir is the phosphate ester prodrug of amprenavir. *Per se*, it has little or no antiretroviral activity but requires in-vivo metabolism to release the active moiety, amprenavir, which is a selective inhibitor of HIV-1 and HIV-2 replication.

- Resistance in vitro

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro*. *In vitro* serial passage experiments have demonstrated that I50V was the key protease mutation associated with amprenavir resistance. Mutation I84V was observed transiently. More recently, protease mutations I54M and V32I + I47V have also been identified during serial passage in the presence of amprenavir.

Genotypic analysis of isolates from patients receiving amprenavir identified mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as mutations in the p7/p1 and p1/p6 gag and gag-pol polyprotein precursor cleavage sites.

Genotypic and phenotypic susceptibility analysis have been performed in the main clinical studies, clinical trials (APV 30002, 30001 and 30003), and the results are presented under the discussion of clinical efficacy of these studies.

Relationship between plasma concentration and antiretroviral activity

The antiviral effect of fosamprenavir and its relationship to the dose was assessed in antiretroviral naïve patients (study APV20001), which is further discussed under the dose ranging studies.

In antiretroviral-experienced patients (study APV30003), no relationship was established between the individual average plasma amprenavir C_{\min} values or individual average plasma C_{\min}/IC_{50} values to the efficacy endpoints.

In this study administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily resulted in plasma amprenavir trough concentrations (geometric mean C_{\min} 1.74 μ g/ml) above the median IC_{50} value reported in this study (0.008 μ g/ml [0.001-0.144]).

Pharmacokinetics

The pharmacokinetics profile was determined in a series of studies mainly in healthy volunteers following single and multiple dose administration of fosamprenavir with or without low dose of ritonavir as a pharmacokinetic enhancer.

After a clean-up step (solid phase-extraction, protein precipitation) samples were analysed by HPLC/MS/MS.

- Absorption - Distribution

Preclinical studies showed that fosamprenavir is almost completely (99 %) hydrolysed to amprenavir at or near the intestinal membrane via alkaline phosphatase prior to reaching the systemic circulation. The rapid and extensive conversion of fosamprenavir to amprenavir has been confirmed in clinical studies (equimolar doses of fosamprenavir and amprenavir achieved equivalent amprenavir AUC values and the fosamprenavir AUC was < 0.6 % of corresponding amprenavir AUC).

Maximum amprenavir peak plasma concentrations were observed approximately 2 hours after single and multiple dose administration of fosamprenavir.

The absolute bioavailability of fosamprenavir in humans has not been established.

A greater than proportional increase in plasma amprenavir AUC_{∞} was observed following fosamprenavir single dose administration of 1395 mg and 1860 mg (AUC_{∞} /dose ratio: 0.019 for the 1395 mg dose and 0.026 for the 1860 mg dose).

Upon repeat dosing of fosamprenavir 1395 mg (molar equivalent of 1200 mg of amprenavir) BID to HIV-infected patients a decrease in amprenavir AUC at steady-state was observed compared with single dose administration ($AUC_{\tau,ss}$: 16.5h* μ g/ml versus AUC_{∞} : 22.8h* μ g/ml).

There were no substantial differences in the pharmacokinetic profile of fosamprenavir in healthy volunteers versus in HIV-infected patients.

The addition of ritonavir 100 mg BID to fosamprenavir 700 mg BID for 14-days increased plasma amprenavir $C_{\max,ss}$ by approximately 51 %, plasma amprenavir $AUC_{\tau,ss}$ by 3.4-fold and $C_{\tau,ss}$ by 12.7-fold compared to values observed after administration of the same dose of fosamprenavir without ritonavir.

When compared to the once daily regimen (fosamprenavir 1400 mg + ritonavir 200 mg), the BID regimen (fosamprenavir 700 mg + ritonavir 100 mg BID) showed higher amprenavir $AUC_{\tau,ss}$, higher C_{\min} (20-30 %) but lower C_{\max} (20-30 %). These improved pharmacokinetics parameters favour a BID regimen.

Food did not alter the pharmacokinetics of fosamprenavir when administered as a tablet with ritonavir and therefore tablets can be taken regardless of food intake.

In contrast a high fat meal taken with fosamprenavir oral suspension reduced the exposure to amprenavir compared to fasted state (decrease of AUC by approximately 29 % and C_{max} 46 %). Therefore the suspension should be administered without food at the same dose as the oral tablet.

It has been demonstrated *in vitro* that amprenavir is a substrate for the counter-transport protein P-glycoprotein.

The apparent oral volume of distribution of amprenavir is approximately 430l suggesting that it penetrates freely into tissues beyond the systemic circulation. This value is decreased when co-administered with ritonavir by approximately 40%, most likely due to an increase in amprenavir bioavailability. *In vitro* the plasma protein binding of amprenavir is approximately 90 %, mainly to α_1 -acid-glycoprotein (AAG) and to a lesser extent to human serum albumin (HSA).

Limited data indicate that amprenavir penetrates into semen. The cerebrospinal spinal fluid to plasma concentration ratio was < 1 %, indicating a poor penetration.

- Metabolism – Elimination

Amprenavir is primarily metabolised by the liver. As demonstrated *in vitro*, the metabolism is *via* cytochrome P450, mainly CYP 3A4 isoenzyme. Amprenavir also inhibits CYP3A4 and potentially is a mild CYP3A4 inducer.

The elimination pathway for amprenavir is mainly through the faeces. Total recovery of a 600 mg dose was 89 % (range 66-93 %) primarily as oxidative metabolites in the urine (approximately 14 %) and in faeces (approximately 75 %). Total excretion of amprenavir in the urine over 24 hours was less than 1 % of the administered dose. Plasma elimination half-life of amprenavir, after fosamprenavir administration is approximately 7.7 hours, which is comparable to that after amprenavir administration. When fosamprenavir is boosted with low dose of ritonavir, the half-life of amprenavir is increased to 15-23 hours.

- Comparison between the clinical trials formulation with the formulations to be marketed

In the early studies, the disodium and the calcium salts were administered both as an oral suspension. The calcium salt 1728 mg (equivalent to 1395 mg fosamprenavir) that delivered an equivalent plasma amprenavir AUC_{∞} , and a 27 % lower C_{max} than amprenavir 1200 mg was selected for further development.

With regard to 700 mg film-coated tablet, as already mentioned in the Quality section of this document, three variants A, B, C have been used in the clinical development programme corresponding to differences in drug substance and drug product scale up and in the drug substance particle size. There was a concern that the mix of these different variants of different exposure (variant B and C exhibiting lower plasma amprenavir exposures: 13 and 16 % in comparison to variant A) might have influenced the efficacy demonstration. To address this concern, the applicant conducted one study (APV10021) showing that scale up of the drug product had no impact in-vivo (see table 1).

Table 1: APV10021 Bioequivalence Analysis

	GLS Mean N = 78		GLS Mean Ratio (90% CI)
	Treatment A1 (Tablet Variant A)	Treatment B2 (Tablet new Variant A)	Treatment B/A
AUC_{∞} (µg.h/ml)	23.76	24.12	1.02 (0.97-1.06)
AUC_{last} (µg.h/ml)	22.51	23.05	1.02 (0.98-1.07)
C_{max} (µg/ml)	5.15	5.38	1.04 (0.98-1.11)

¹ Treatment A: 2 oral film-coated 700mg tablets (variant A used in APV 10015), unmilled drug substance manufactured at 45 kg scale and drug product manufactured at pilot scale

² Treatment B: 2 oral film-coated 700mg tablets (new variant A), unmilled drug substance manufactured at 45 kg scale and drug product manufactured at production scale

In addition the applicant performed a randomised, open-label, two-period, balanced crossover study (APV10029) which compared the steady-state plasma amprenavir pharmacokinetics between fosamprenavir Tablet Variants A and C, when each was administered as 1400 mg once daily in combination with ritonavir 200 mg once daily in healthy volunteers. As displayed in table 2, steady-state plasma amprenavir C_{max} , $AUC_{(0-\tau)}$, and C_{τ} values were equivalent for fosamprenavir Tablet Variants A and C under these conditions.

Table 2: APV10029 Bioequivalence Analysis

Plasma APV Steady-State PK Parameter	GLS Mean N=70		GLS Mean Ratio (90% CI)
	Treatment A1 (Tablet new Variant A)	Treatment B2 (Tablet Variant C)	Treatment B/A
AUC(0- τ) ($\mu\text{g}\cdot\text{h}/\text{ml}$)	65.38	64.50	0.99 (0.96-1.02)
C_{max} ($\mu\text{g}/\text{ml}$)	7.21	7.24	1.00 (0.97-1.04)
C_{τ} ($\mu\text{g}/\text{ml}$)	1.26	1.21	0.96 (0.92-1.01)

¹ Treatment A: 2 oral film-coated 700mg tablets OD, unmilled drug substance manufactured at 45kg scale and drug product manufactured at production scale (new Variant A), plus ritonavir 200mg OD for 14 days

² Treatment B: 2 oral film-coated 700mg tablets OD, milled drug substance manufactured at 200kg scale and tablets manufactured at production scale (Variant C), plus RTV 200mg OD for 14 days.

No clinical impact from the concomitant use of the different variants is therefore expected in the pivotal studies APV30002 and APV30003 since fosamprenavir was boosted with ritonavir. Only tablet variant C will be marketed which is acceptable as fosamprenavir is recommended to be used with ritonavir.

The oral suspension delivered an equivalent plasma amprenavir AUC_{∞} and a 14% higher C_{max} relative to the tablet formulation under fasting conditions (means ratio: 1.145, 90 % CI: 1.011-1.297).

- Special populations

Pooled data from the different studies did not reveal any influence of gender, race, weight or age on the pharmacokinetics of fosamprenavir.

Pharmacokinetics studies in paediatric population using the oral suspension are ongoing and the results will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

No specific studies have been performed in the elderly.

Considering the small portion of the dose recovered in the urine, no specific study was performed in patients with renal impairment and no dosage adjustment is considered necessary in these patients as mentioned in the Summary of Product Characteristics.

There are currently no data in patients with hepatic impairment. Therefore fosamprenavir boosted with ritonavir should be administered with caution in patients with mild and moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment. Data to support the use of fosamprenavir in patients with various degrees of hepatic impairment will be submitted as part of the follow-up measures to be fulfilled post-authorisation

- Interaction studies

Amprenavir and ritonavir are both substrate and inhibitor of CYP3A4, with ritonavir being more potent inhibitor than amprenavir. Amprenavir is potentially a mild CYP3A4 inducer and is a substrate and inducer of P-gp. Ritonavir also inhibits CYP2D6 and induces CYP3A4, CYP1A2, CYP2C9 and glucuronosyl transferase. Fosamprenavir solubility is also significantly reduced at pH greater than 5.

Therefore co-administration of fosamprenavir/ritonavir with substances that interact with CYP450, P-gp or that increases gastrointestinal pH may result in interaction. Several studies have therefore been performed and the main findings can be summarised as follows:

Interaction with antiretroviral medicinal products

Efavirenz

When efavirenz 600 mg is co-administered with fosamprenavir boosted with ritonavir as a once daily regimen, there was a decreased in plasma amprenavir C_{\min} by 36 % while AUC and C_{\max} were not significantly altered. However when fosamprenavir 700 mg BID with ritonavir 100 mg BID was used concomitantly with efavirenz there was no clinically relevant interaction, even if slightly trough amprenavir values were lower (-17 %). No dosage adjustment is therefore considered necessary when the recommended fosamprenavir twice-daily dosing regimen boosted with ritonavir is co-administered with efavirenz.

Lopinavir/ritonavir

Co-administration of fosamprenavir (700 mg BID) boosted with ritonavir (100 mg BID) with lopinavir/ritonavir (400 mg/100 mg) resulted in reduced C_{\max} (- 58 %), AUC (- 63 %) and C_{\min} (- 65 %) of amprenavir and in increased lopinavir C_{\max} (+ 30 %), AUC (+ 37 %) and C_{\min} (+ 52 %).

When fosamprenavir (without ritonavir) (1400mg BID) was co-administered with lopinavir/ritonavir at increased dose (lopinavir/ritonavir 533/33 mg BID) there was no alteration of lopinavir pharmacokinetic parameters however there was also a decrease in C_{\max} (- 13 %), AUC (- 26 %) and C_{\min} (- 42 %) of amprenavir.

A further investigation has been performed with three different regimens:

- 1) fosamprenavir 700mg BID + lopinavir 400mg/ritonavir 100mg BID
- 2) fosamprenavir 700mg BID + ritonavir 100mg BID administered 4 hours prior to lopinavir 400mg/ritonavir 100mg BID
- 3) fosamprenavir 1400mg OD + ritonavir 200mg OD administered 12 hours prior to lopinavir 800mg/ritonavir 200mg OD.

Preliminary data suggest that for all three regimens, plasma amprenavir concentrations were lower than historical control data for fosamprenavir 700 mg BID with ritonavir 100 mg BID. The treatments that included separation of dosing along with increased ritonavir doses did not appear to improve plasma amprenavir pharmacokinetics, although lopinavir concentrations appeared to be maintained.

Overall, these studies do not allow drawing adequate dosage recommendations. In-vitro investigations suggest that induction and inhibition of metabolic and potentially transport processes play a role in the potential mechanism for this interaction. As some heavily treatment-experienced patients might benefit from a salvage regimen containing lopinavir/ritonavir and fosamprenavir these data have been reflected in the Summary of Product Characteristics highlighting that appropriate dose of the combination has not yet been defined in terms of efficacy and safety.

Potential interaction between fosamprenavir boosted with ritonavir and other protease inhibitors has not been studied.

Nevirapine

Based on its effects on other protease inhibitors, nevirapine might decrease serum concentration of amprenavir when co-administered with fosamprenavir boosted with ritonavir. Therefore the applicant is committed to perform an interaction study to establish an appropriate dosage recommendation, the results of which will be submitted post-authorisation.

No specific interaction study has been performed with NRTIs, however the applicant undertook to provide data on the co-administration between fosamprenavir with ritonavir and tenofovir disoproxil fumarate, as part of the follow-up measures to be fulfilled post-authorisation

Interaction with other medicinal products

Antacid suspension and ranitidine

Both antacid suspension (equivalent to 3.6 grams aluminium hydroxide and 1.8 grams magnesium hydroxide) and ranitidine (300 mg single dose) decreased amprenavir AUC by 18 % and 30 % and C_{\max} by 35 % and 51 % respectively when fosamprenavir (1400 mg) was co-administered without ritonavir. However, no dosage adjustments are considered necessary since C_{\min} was not altered.

This also applies to proton pump inhibitors, which are expected to modify the amprenavir pharmacokinetics parameters to the same extent.

Atorvastatin

Fosamprenavir with ritonavir (700 mg + 100 mg BID for 2 weeks) co-administered with atorvastatin (10 mg once daily for 4 days) did not alter the C_{max} , AUC and C_{min} of amprenavir whereas atorvastatin C_{max} (+184 %), AUC (+130 %), C_{min} (+73 %) were markedly increased. A dose reduction of atorvastatin is therefore recommended with careful monitoring for atorvastatin toxicity.

Other interactions

By extrapolation from the data previously obtained with amprenavir, grapefruit juice is not expected to significantly alter amprenavir pharmacokinetics, as stated in the Summary of Product Characteristics.

Additional interactions studies of fosamprenavir boosted with ritonavir with oral contraceptives, ketoconazole, rifabutin and methadone will be performed by the applicant, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Clinical efficacy

An overview of the main clinical studies submitted to support the efficacy and safety of fosamprenavir in HIV infected adults is displayed in table 3.

Table 3: Overview of main clinical studies with fosamprenavir

Study	Population	Treatment	N Treated patients	Endpoint
Main studies				
APV30002 908 boosted with RTV and OD	Antiretroviral naïve patients	Treatment 1: 908 1400mg OD + RTV 200mg OD + ABC 300mg BID + LAM 150mg BID Treatment 2: NFV 1250mg BID + ABC 300mg BID + LAM 150mg BID	908/RTV N=322 NFV N=327	A lower limit of the 95% confidence interval of the difference between 908/RTV and NFV in term of % of patients with undetectable viral load LOQ 400 copies/ml at 48 weeks of greater than -12% would demonstrate non inferiority
APV30001 (supportive) 908 unboosted and BID	Antiretroviral naïve patients	Treatment 1: 908 1400mg BID + ABC 300mg BID + LAM 150mg BID Treatment 2: NFV 1250mg BID + ABC 300mg BID + LAM 150mg BID	908 N=166 NFV N=83	With an upper limit of the 95% confidence interval for the difference between 908 and NFV in mean AAUCMB less than 0.5 log ₁₀ copies/ml, non inferiority would be demonstrated at 48 weeks.
APV30003 908 boosted with RTV OD or BID	Antiretroviral experienced patients	Treatment 1: 908 700mg BID + RTV 100mg BID + two active RTIs Treatment 2: 908 1400mg OD + RTV 200mg OD + two active RTIs Treatment 3: LPV 400mg/RTV 100mg BID + two active RTIs	908/RTVOD N=105 908/RTVBID N=107 LPV/RTV N=103	With an upper limit of 97.5% confidence interval of the difference in mean AAUCMB for log ₁₀ plasma HIV-1 RNA at 24 and 48 weeks less than 0.5 log ₁₀ copies/ml between 908/RTV OD and LPV/RTV and 908/RTV BID and LPV/RTV would demonstrate non inferiority).

908 = fosamprenavir; RTV = ritonavir; NFV = nelfinavir; ABC = abacavir; LAM = lamivudine and LPV = lopinavir; OD = once daily; BID = twice daily and LOQ = Limit of quantification; AAUCMB = Average area under the curve minus baseline.

- Dose response study(ies)

Considering that fosamprenavir is a prodrug of amprenavir, the dose selection was mainly supported by comparison between fosamprenavir and amprenavir.

A relationship between plasma amprenavir exposure following fosamprenavir administration and antiviral activity was first established in study APV20001. This study demonstrated that both fosamprenavir doses 1395 mg (molar equivalent to 1200 mg of amprenavir) or 1860 mg (molar equivalent to 1600 mg of amprenavir) BID delivered plasma steady state amprenavir pharmacokinetics, short term (4 week) safety and antiviral activity (around 2 log copies/ml reduction in HIV plasma RNA concentrations) comparable to 1200 mg amprenavir BID when administered with abacavir 300 mg BID and lamivudine 300 mg BID in HIV infected patients.

A new dosage regimen for amprenavir has been recommended to maximise plasma exposures: amprenavir 600 mg boosted with 100 mg ritonavir. The chosen dosing regimen studied in the phase III studies (700 mg fosamprenavir + 100 mg ritonavir BID or 1400 mg fosamprenavir + 200 mg ritonavir OD) was therefore based on a molar equivalent dose with 600 mg amprenavir +100 mg ritonavir BID or 1200 mg amprenavir + 200 mg ritonavir OD. However there was a concern pertaining to the dose justification mainly based on extrapolation from pharmacokinetics data with amprenavir unboosted with ritonavir and to the lack of direct comparison between amprenavir + ritonavir and fosamprenavir + ritonavir.

This concern was addressed by the provision of study APV10022, a phase I, multiple-dose, randomised, open-label, two-period, four-arm, balanced crossover study in which amprenavir (600 mg BID) was given with and without ritonavir (100 mg BID) and compared with fosamprenavir (700 mg BID) with and without ritonavir (100 mg BID) for 14 days.

Results, as displayed in the table 4 below, showed comparable pharmacokinetic exposure achieved between amprenavir and fosamprenavir when boosted with ritonavir, with plasma trough concentrations above IC₅₀.

Table 4: Plasma APV PK Parameters

Plasma APV PK Parameter	Geometric Mean (95% CI)			
	APV 600 mg BID for 14 days	APV 600 mg BID + RTV 100 mg BID for 14 days	FPV 700 mg BID for 14 days	FPV 700 mg BID + RTV 100 mg BID for 14 days
AUC _{τ,ss} (µg.h/ml)	8.21 (6.38 – 10.6)	26.2 (22.3 – 30.9)	9.51 (7.81 – 11.6)	33.2 (28.0 – 39.5)
C _{max,ss} (µg/ml)	3.66 (2.76 – 4.84)	4.69 (3.97 – 5.54)	3.19 (2.64 – 3.85)	4.92 (4.19 – 5.77)
C _{τ,ss} (µg/ml)	0.122 (0.071 – 0.207)	1.32 (1.11 – 1.57)	0.135 (0.099 – 0.183)	1.77 (1.48 – 2.13)

APV = amprenavir; RTV = ritonavir ; FPV = fosamprenavir
Each fosamprenavir oral film-coated 700 mg tablet is the molar equivalent of 600 mg APV

- Main study (ies)

Studies in antiretroviral treatment-naïve adult patients: Studies APV 30002 (APV 30005) and APV 30001

Study APV 30002

This was a multicentre, randomised, open-label, two arms study designed to evaluate the safety and antiviral efficacy of fosamprenavir boosted with ritonavir OD versus nelfinavir BID in combination with abacavir and lamivudine both as BID.

Patients were antiretroviral-naïve (i.e., fewer than 4 weeks of previous therapy with a NRTI and no previous exposure to any PI or NNRTI) and were stratified according to plasma HIV-1 RNA level at screening (≥ 1000 -10,000 copies/ml; $> 10,000$ -100,000 copies/ml; or $> 100,000$ copies/ml).

Treatments

Patients were randomised in a 1:1 ratio to receive either:

- fosamprenavir 1400 mg OD with ritonavir 200 mg OD + abacavir 300 mg BID + lamivudine 150 mg BID (referred to as fosamprenavir boosted OD group), or;
- nelfinavir 1250 mg BID + abacavir 300 mg BID + lamivudine 150 mg BID (referred to as nelfinavir BID group).

Patients were to continue on randomised therapy until the last patients enrolled completed their week 48 visit unless they met a protocol defined switch criteria (plasma HIV-1 RNA result > 1,000 copies/ml at week 12 or thereafter). Patients changing their randomised PI or adding a NNRTI because of virological failure entered the non-randomised phase of the study. Patients changing their background NRTI therapy due to intolerance remained in the randomised phase.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of patients with plasma HIV-1 RNA levels < 400 copies/ml at 48 weeks.

Secondary efficacy endpoints included the proportion of subjects with plasma HIV-1 RNA levels < 400 copies/ml at 24 weeks and <50 copies/ml at 24 and 48 weeks; time to treatment failure; change from baseline in plasma HIV-1 RNA levels over time; and change from baseline in CD4+ cell counts over time.

Sample size

The primary analysis assessed the non-inferiority of fosamprenavir boosted OD to nelfinavir BID with respect to the proportion of patients achieving a plasma HIV-1 RNA level < 400/ml copies at week 48. The applicant justified the choice of the non-inferiority margin of 12 %.

Statistical methods

The intent-to treat exposed (ITT (E)) population was the primary population for the efficacy analyses (all patients randomised with documented evidence of having received at least one dose of randomised treatment). The secondary population was the per protocol (PP) where randomised patients who had no on-treatment post-baseline efficacy data or who had major protocol violations were excluded.

Rebound or Discontinuation = Failure (RD=F); Patients were considered as failures (non-responders) if they never achieved virologic suppression (<400 copies/ml or <50 copies/ml as appropriate) by the designated timepoint, or following initial suppression the viral load rebounded (> 400 copies/ml or > 50 copies/ml on two consecutive occasions). Patients with missing values were only considered failures if they were considered a failure at either the previous or subsequent visit. Patients were also considered as failures if they discontinued randomised study medication for any reason.

Missing or Discontinuation = Failure (MD=F)

Patients were considered as failures (non-responders) if they never achieved virologic suppression (<400 copies/ml or <50 copies/ml as appropriate) by the designated timepoint, or following initial suppression the viral load rebounded (> 400 copies/ml or > 50 copies/ml on at least one occasion). Patients were considered as failures if they had a missing value at the designated timepoint irrespective of available values at previous or subsequent visits.

Patients were considered as failures if they discontinued randomised study medication for any reason.

In this study, for both RD=F and the MD=F analyses, patients who met the protocol defined switch criterion and elected to change therapy were considered as having discontinued randomised therapy, whether the PI component of the regimen changed or only the background RTI therapies changed.

However, subjects changing background therapies due to intolerance (e.g. hypersensitivity to abacavir) were not considered as having discontinued randomised therapy

Observed analysis: Only subjects with data at a visit were included in the analysis and no missing values were imputed.

RESULTS

Participant flow

The population enrolled was mostly male (73 %), white (53 %), had a viral load of approximately 4.8 log₁₀ copies/ml (with a significant proportion of patients (43%) with a viral load >100 000 copies/ml, and 16% > 500 000 copies/ml) and a CD4 cell count of approximately 170/mm³ (55% with CD4 cell count < 200/mm³), with 22% being CDC stage C. Intravenous drug users were allowed to be enrolled (14 %) as well as HBV- HCV co-infected patients.

A total of 660 patients were randomised. Of these, 649 patients received at least one dose of study drug: 322 (50%) in the fosamprenavir boosted OD group and 327 (50%) in the nelfinavir BID group. Four hundred and seventy three subjects (73%) completed at least 48 weeks of randomised treatment.

A significant number of patients experienced premature discontinuation at 48 weeks (27%). Among the reasons for premature discontinuations a higher rate of protocol switch criterion in the nelfinavir arm (8 % versus < 1 %) and a higher rate of adverse events in the fosamprenavir boosted OD arm were observed (9 % versus 5 %).

Outcomes and estimation

The results on the primary endpoint at weeks 48 are displayed in table 5:

Table 5: Proportion of patients with plasma HIV-RNA < 400 copies/ml at week 48

Population	908/RTV OD % (n/N)	NFV BID % (n/N)	Stratified Difference	95 % CI
ITT(E) RD=F	69 (221/322)	68 (221/327)	1 %	-6 %, 8 %
ITT(E) MD=F	68 (220/322)	65 (213/327)	3 %	-4 %, 10 %
ITT(E) Observed	95 (222/234)	90 (234/261)	5 %	0 %, 10 %
Per-Protocol	95 (215/226)	91 (215/237)	4 %	0 %, 9 %

908 = fosamprenavir; RTV = ritonavir. NFV = nelfinavir; ITT = intent to treat;
RD=F = Rebound or Discontinuation = Failure; MD=F = Missing or Discontinuation = Failure

Results in the ITT and per protocol analyses were in accordance with the 12 % predefined non-inferiority margin (lower limit of 95% confidence interval of the difference between fosamprenavir boosted OD and nelfinavir in term of percentages of patients with viral load less than 400 copies/ml above -12).

Results were always in favour of the fosamprenavir boosted OD arm and the 48 weeks data allowed a reliable interpretation of the durability of the antiviral activity.

Virological failure was greater in the nelfinavir group (17%) than in the fosamprenavir boosted OD group (7%). No genotypic or phenotypic amprenavir resistance was detected in virus from 32 patients failing fosamprenavir boosted OD. A significantly higher proportion of nelfinavir treated patients acquired primary or secondary PRO mutations (27/54 (50 %; p < 0.001). Treatment emergent NRTI resistance was significantly less frequent with fosamprenavir boosted (4/32; 13 %) compared to nelfinavir treated patients (31/54; 57 %) (p < 0.001). According to the applicant, failures in the fosamprenavir boosted OD arm were likely due to a lack of adherence, therefore without significant emergence of resistance, whereas the failures to nelfinavir were mainly explained by insufficient virological suppression with emergence of resistance.

Study APV 30005

This non-comparative, open-label rollover protocol included those patients who had completed 48 weeks or more on study APV 30002 with the objective to report the long-term antiviral response, safety and tolerability of a fosamprenavir boosted OD. Of the 322 patients who received fosamprenavir boosted with ritonavir OD in APV30002, 210 patients rolled over to APV30005 and continued to receive fosamprenavir boosted OD.

Results

Of the 210 enrolled patients, 19 (9 %) prematurely discontinued, mainly due to consent withdrawal (2 %) and adverse events (2 %).

Results are displayed in table 6:

Table 6: Proportion of Subjects in APV30002/APV30005 with Plasma HIV-1 RNA <400 copies/ml and 50 copies/ml by Plasma HIV-1 RNA levels at APV30002 Screening fosamprenavir boosted OD Population (Observed Analysis)

Plasma HIV-1 RNA Stratum	400 copies/ml			50 copies/ml		
		908/RTV OD N=210 % (n/N)			908/RTV OD N=210 % (n/N)	
	Week 24	Week 48	Week 96	Week 24	Week 48	Week 96
<10,000 copies/ml	100 (16/16)	100 (16/16)	100 (10/10)	94 (15/16)	88 (14/16)	100 (10/10)
>10,000 - 100,000 copies/ml	>99 (108/109)	96 (106/110)	98 (56/57)	83 (90/109)	85 (93/110)	89 (51/57)
>100,000 copies/ml	95 (77/81)	94 (76/81)	93 (43/46)	46 (37/81)	68 (55/81)	78 (36/46)
>100,000 250,000	95 (18/19)	95 (19/20)	93 (13/14)	63 (12/19)	85 (17/20)	93 (13/14)
>250,000 500,000	100 (25/25)	100 (24/24)	100 (14/14)	56 (14/25)	67 (16/24)	79 (11/14)
>500,000	92 (34/37)	89 (33/37)	89 (16/18)	30 (11/37)	59 (22/37)	67 (12/18)
Total Population	98 (201/206)	96 (198/207)	96 (109/113)	69 (142/206)	78 (162/207)	86 (97/113)

908 = fosamprenavir; RTV = ritonavir

The above results suggest a durability of the antiviral response although these should be taken with caution in view of the design of the study.

Study APV 30001

This randomised, parallel group, 2 arms, open label study is considered more as supportive than confirmatory since fosamprenavir was used unboosted.

Patients were randomised 2:1 to either receive fosamprenavir 1400 mg BID or nelfinavir 1250 mg BID, when administered in combination with abacavir 300 mg BID and lamivudine 150 mg BID. The study was primarily designed to provide safety data on fosamprenavir, and was statistically powered on the endpoint of plasma HIV-1 RNA average area under the curve minus baseline (AAUCMB), a secondary endpoint. The primary endpoint was the proportion of patients with plasma HIV RNA < 400 copies/ml at week 24 and 48.

A total of 249 patients were randomised and received treatment with fosamprenavir BID (n = 166) or nelfinavir BID (n = 83). Most patients were male and American Hispanic or Black. The median plasma HIV-1 RNA levels was 4.83-log₁₀ copies/ml, the median baseline CD4 cell count was 212 cells/mm³ at baseline and 20 % of patients had a prior history of a CDC Class C event.

Results

Table 7: % of patients with HIV-RNA <400 copies/ml at 48 weeks

Population	908 BID % (n/N)	NFV BID % (n/N)	Stratified Difference	95 % CI
ITT(E) Population (RD=F)	66 (109/166)	51 (42/83)	15 %	(2 %, 28 %)
ITT(E) Population (MD=F)	66 (109/166)	48 (40/83)	17 %	(5 %, 30 %)
ITT(E) Observed	92 (109/118)	93 (41/44)	-1 %	(-10 %, 9 %)
Per-Protocol Population	94 (104/111)	95 (40/42)	-1 %	(-10 %, 7 %)

908 = fosamprenavir; NFV = nelfinavir; ITT(E) = intent to treat exposed;

RD=F = Rebound or Discontinuation = Failure; MD=F = Missing or Discontinuation = Failure

In the ITT (RD = F) analysis, the proportion of patients with plasma HIV-1 RNA <400 copies/ml at Week 48 was greater in the fosamprenavir BID group than in the nelfinavir BID group. Among patients with a history of hepatitis C, the proportion of patients with plasma HIV-1 RNA < 400 copies/ml at Week 48 was comparable between the treatment groups (fosamprenavir BID: 48 %; nelfinavir BID: 46 %). There was a larger number of patients meeting a criterion for virological failure in the nelfinavir BID group (28%) in comparison with the fosamprenavir group (14 %). Similar proportions of patients were considered as failures due to prematurely discontinuing their randomised PI due to an adverse event (fosamprenavir BID: 5 %; nelfinavir BID: 6 %). The significant number of premature discontinuation (fosamprenavir BID: 30%; nelfinavir BID: 46%) precludes therefore reliable interpretation of the data.

Studies in antiretroviral treatment-experienced adult patients: Study APV 30003

This is a phase III randomised, parallel group, three-arm, open-label study to compare the safety and efficacy of OD and BID dosing regimens of fosamprenavir boosted with ritonavir versus lopinavir/ritonavir in combination with two active RTIs.

Patients were antiretroviral experienced i.e. previous experience with one or two protease inhibitor(s) (ritonavir given at a dose \leq 400 mg in combination with another PI was counted as one PI; a PI taken alone and later in a ritonavir boosted regimen was counted as two different PIs); received at least 12 consecutive weeks of prior protease inhibitor therapy (up to two prior PIs), with documented virological failure on a prior PI regimen, defined as having plasma HIV-1 RNA that never went below 1000 copies/ml after at least 12 consecutive weeks of PI therapy, or initial suppression of HIV-1 RNA which subsequently rebounded to \geq 1000 copies/ml.

Patients had plasma HIV RNA viral load \geq 1000 copies/ml and were stratified at screening. There were no prerequisite in term of CD4 cell counts.

In line with the CPMP “Note for Guidance on the clinical development of medicinal products for treatment of HIV infection”, hepatitis co-infected patients could have been enrolled. However co-infected patients could enter provided that they had no history of clinically relevant or hepatitis within the previous 6 months. Intravenous drug users, who are expected to exhibit a lesser compliance, could also be enrolled.

Outcomes/endpoints

The primary efficacy endpoint was average area under the curve minus baseline (AAUCMB) in log₁₀ plasma HIV-1 RNA at 24 and 48 weeks.

Secondary efficacy endpoints included:

- change from baseline in log₁₀ plasma HIV-1 RNA over 24 and 48 weeks;
- proportion of patients with plasma HIV-1 RNA levels < 400 and < 50 copies/ml over 24 weeks and 48 weeks;
- time to treatment failure; this was defined as the number of days from the first dose of study medication (Study Day 1) to the first of the following events: confirmed plasma HIV-1 RNA above 400 copies/ml, permanent discontinuation of randomized therapy, HIV disease progression or death. To be a confirmed plasma HIV-1 RNA above 400 copies/ml the patient should have had two values above 400 following two values below 400; patients who never went below 400 were considered to be treatment failures at Day 1. A similar definition based around 50 copies/ml was used to calculate “time to treatment failure (50 copies/ml)” and a similar definition based around achieving 1 log copies/ml below baseline was used to calculate “time to treatment failure (1 log copies/ml below baseline)”
- proportion of patients with \geq 1.0 log₁₀ decrease in HIV-1 RNA at 24 and 48 weeks;
- change from baseline and AAUCMB in CD4+ cell count over 24 weeks and 48 weeks.

Sample size

The primary analyses of this study assessed the non-inferiority of each of the two fosamprenavir boosted with ritonavir arms to the control arm with respect to AAUCMB in plasma HIV-1 RNA at 24,

then 48 weeks. A non-inferiority margin of 0.5-log₁₀ copies/ml was considered appropriate. To provide approximately 90 % power to perform each of these tests at the 1.25% significance level (that is by using two-sided 97.5% confidence intervals to assess non-inferiority), assuming a standard deviation in plasma HIV-1 RNA of 0.85 log₁₀ copies/ml, 72 patients were required in each arm. This has been increased to a minimum of 82 to adjust for patients discontinuing prematurely. The width of the confidence intervals accounted for the multiple comparisons; the combined significance level of the two tests was no more than 2.5 %.

Results

Patients' disposal

Overall, the population enrolled had a median age of 40 years, was mostly male and White. A limited proportion of women have been enrolled in this study 15%. Patients had a viral load of approximately 4-log₁₀ copies/ml (only 12% of patients had a viral load > 5 log₁₀ copies/ml) and a CD4 cell count of approximately 260/mm³ (33% with CD4 cell count <200/ mm³), with a significant proportion being CDC stage C (33%).

The population mainly consists of patients with moderate antiretroviral experience. Only 65% of patients were receiving a PI therapy at entry. There is a trend for more extensive prior PI experience in the fosamprenavir-boosted arms in particular in the once daily regimen (≥ 2 PIs taken: fosamprenavir boosted OD: 57% versus fosamprenavir boosted BID: 49% and lopinavir/ritonavir: 40%). The median durations of prior exposure to NRTIs were 257 weeks for patients receiving fosamprenavir with ritonavir twice daily (79 % had ≥ 3 prior NRTIs) and 210 weeks for patients receiving lopinavir/ritonavir (64 % had ≥ 3 prior NRTIs). The median durations of prior exposure to protease inhibitors were 149 weeks for patients receiving fosamprenavir with ritonavir twice daily (49 % received ≥ 2 prior PIs) and 130 weeks for patients receiving lopinavir/ritonavir (40 % received ≥ 2 prior PIs).

At 48 weeks, 23% of patients experienced premature discontinuation of the randomised PI.

Efficacy results

The results on the primary endpoint are displayed in table 8:

Table 8: Summary of Plasma HIV-1 RNA AAUCMB Values (log₁₀ copies/l) at Week 24 and 48

Population		908/RTV OD Mean (n)	908/RTV BID Mean (n)	LPV/RTV BID Mean (n)	Mean Diff ^a (97.5% CI) 908/RTV OD vs LPV/RTV BID	Mean Diff ^b (97.5% CI) 908/RTV BID vs LPV/RTV BID
ITT(E) Observed	Week 24	-1.48 (104)	-1.50 (105)	-1.65 (103)	0.184 (-0.065, 0.433)	0.171 (-0.082, 0.424)
	Week 48	-1.49 (104)	-1.53 (105)	-1.76 (103)	0.267 (-0.017, 0.551)	0.244 (-0.047, 0.536)
ITT(E) D=BL	Week 24	-1.44 (104)	-1.47 (105)	-1.61 (103)	0.172 (-0.087, 0.431)	0.151 (-0.113, 0.415)
	Week 48	-1.42 (104)	-1.46 (105)	-1.67 (103)	0.252 (-0.049, 0.553)	0.225 (-0.083, 0.533)
ITT(E) LOCF	Week 24	-1.47 (104)	-1.50 (105)	-1.68 (103)	0.208 (-0.047, 0.463)	0.188 (-0.068, 0.443)
	Week 48	-1.48 (104)	-1.53 (105)	-1.77 (103)	0.292 (-0.007, 0.590)	0.257 (-0.044, 0.557)
Per-Protocol	Week 24	-1.56 (84)	-1.64 (76)	-1.74 (78)	0.195 (-0.081, 0.472)	0.131 (-0.143, 0.405)
	Week 48	-1.78 (68)	-1.79 (72)	-1.95 (73)	0.132 (-0.175, 0.440)	0.153 (-0.163, 0.470)

^aEstimate of mean strata- adjusted treatment difference (908/RTV OD - LPV/RTV BID) and 97.5% stratified confidence interval.

^bEstimate of mean strata- adjusted treatment difference (908/RTV BID - LPV/RTV BID) and 97.5% stratified confidence interval.
908 = fosamprenavir; RTV = ritonavir; LPV = Lopinavir; ITT (E) = intent to treat exposed population; D = BL = Discontinuation = baseline; LOCF = Last observation carried forward

At week 24 in the ITT and per protocol analyses, the results were in accordance with the predefined non-inferiority margin (upper limit of 97.5 % confidence interval below 0.5 log₁₀ copies/ml).

However, the point estimates of the difference were always in favour of the lopinavir/ritonavir arm. At week 48, in the ITT, LOCF and PP analyses for the primary efficacy variable, lopinavir/ritonavir is consistently at least numerically superior to the two fosamprenavir + ritonavir arms. This is especially noticeable in the difficult-to-treat population with high (>100 000 copies) viral load at baseline.

These considerations apply for both fosamprenavir boosted regimens, but are even more critical for the OD regimen (which has been shown to exhibit slightly lower Cmin). The Kaplan Meier survival plot of time to treatment (virologic) failure censoring all patients other than those considered to be virologic failures indicated a higher likelihood of a shorter time to treatment failure in the fosamprenavir boosted OD group relative to the fosamprenavir boosted BID and lopinavir/ritonavir BID groups. The distribution of time to treatment failure from Week 24 to Week 48 tends to become similar between the fosamprenavir boosted BID and lopinavir/ritonavir BID groups, even though more patients were classified as treatment failures at Day 1 in the fosamprenavir boosted BID group.

The significant percentage of premature discontinuation (23 %) and the imbalance in the rate of premature discontinuation between the fosamprenavir boosted (26 %) and lopinavir/ritonavir (17 %) arms, might have contributed to the failure in the non-inferiority demonstration. However, the reasons for premature discontinuations are different. For lopinavir/ritonavir they are mainly due to AEs, however for the fosamprenavir/ritonavir they are mainly due to virological failure in fosamprenavir-boosted arms (11% to be compared to <1 % in the lopinavir/ritonavir arm).

When considering the secondary endpoints, especially the more pertinent criteria (closer to the clinical practice) of the percentage of patients with undetectable viral load (< 400 copies/ml), the estimated differences are in favour of the Kaletra arm (table 9).

Table 9: Summary of Proportion of subjects with plasma HIV-1 RNA < 400 copies/ml at Week 24 and 48

Population		908/RTV	908/RTV	LPV/RTV	Stratified Diff ¹	Stratified Diff ¹
		OD	BID	BID	(95% CI)	(95% CI)
		% (n/N)	% (n/N)	% (n/N)	908/RTV OD vs	908/RTV BID vs
					LPV/RTV BID	LPV/RTV BID
ITT(E) RD=F	24 weeks	58 (61/105)	60 (64/107)	69(71/103)	-11%	-8%
	48 weeks	50 (52/105)	58 (62/107)	61 (63/103)	(-24%, 2%)	(-21%, 4%)
ITT(E) M=F	24 weeks	60 (63/105)	60(64/107)	71(73/103)	-12%	-2%
	48 weeks	50 (53/105)	56 (60/107)	63 (65/103)	(-25%, 2%)	(-15%, 11%)
ITT(E) observed	24 weeks	65 (63/97)	72 (64/89)	79 (73/92)	-11%	-10%
	48 weeks	64 (53/83)	75 (60/80)	75 (65/87)	(-24%, 2%)	(-23%, 3%)
Per-Protocol	24 weeks	68 (57/84)	75 (57/76)	82 (64/78)	-13%	-6%
	48 weeks	66 (45/68)	76 (55/72)	78 (57/73)	(-26%, 1%)	(-19%, 7%)
					-14%	-7%
					(-27%, -2%)	(-19%, 6%)
					-12%	0%
					(-26%, 2%)	(-13%, 13%)
					-14%	-5%
					(-27%, -1%)	(-18%, 8%)
					-14%	-2%
					(-28%, 1%)	(-15%, 12%)

The descriptive analyse of CD4 cell count changes from baseline did not favour a difference between the two arms.

The virological substudy showed that 58% (19/33) versus 25% (7/28) patients acquired primary and or secondary PRO mutations in the fosamprenavir with ritonavir arm versus the lopinavir/ritonavir arm. The overall emergence of protease resistance-associated mutations was slightly higher in the fosamprenavir boosted BID arm (OD 17/39 (44%) vs BID 19/33 (58%)). There was however a higher incidence of development of primary protease mutations in the fosamprenavir boosted BID arm (OD 5/17 (29%) vs BID 15/19 ((79%)), whereas in the fosamprenavir boosted OD arm there was a higher incidence of development of only secondary protease mutations (OD 12/17 (71%) vs BID 4/19 (21%)). There was a slight imbalance in the baseline characteristics which may explain why the BID arm might have been of higher risk of emergence of resistance (greater number of patients with

reduced susceptibility to study PI in BID versus OD arms (n=17 versus n=12 respectively) and a slightly higher proportion of patients (10 versus 3) with very high viral load (>250 000 copies/ml).

The majority of protease mutations emerged in the fosamprenavir-boosted groups was mutations previously associated with amprenavir resistance (I50V n=3, I54L n=7, I54M n=3, I84V n=11, V32I n=3, I47V n=5) or associated accessory mutations (L10F n=9, L10I n=3, L33F n=8, M46I/L n=10, A71V/T n=3, V82I n=4). The I50V mutation was only observed in the fosamprenavir boosted BID group and not the fosamprenavir boosted OD group. A higher incidence of I84V was also observed in the fosamprenavir boosted BID group (7/33, 21%) versus the fosamprenavir boosted OD group (4/42, 10%). Emergence of M46I/L was higher in the fosamprenavir boosted BID group (9/33, 27%) versus the fosamprenavir boosted OD group (1/42, 2%).

With amprenavir, a reduction in virological response was observed in the presence of four or more among the following mutations L10F/I/V, K20R/M, E35D, R41K, I54V, L63P, V82A/S/T/S and I84V derived from the Marcelin algorithm (Marcelin AG et Al. *Antimicrob Agents Chemother* 2003 Feb 47:2 594-600).

- Clinical studies in special populations

Studies are ongoing to evaluate the efficacy and safety of fosamprenavir administered with low dose of ritonavir in children the results of which would be submitted as part of the follow-up measures to be fulfilled post-authorisation.

- Supportive studies

Study APV 40003

This is an ongoing open label, single arm, non-randomised study performed in multicentres in Germany to describe the antiviral response and serious adverse events reported with fosamprenavir boosted with ritonavir in antiretroviral combination therapy in heavily pretreated HIV-infected patients.

At the time of the data cut-off (16 weeks), 148 patients were entered. Of these, 65 patients had the opportunity to receive at least 16 weeks of treatment. However after excluding patients who had no prior PI therapy or had previously received amprenavir, 39 pre-treated patients were analysed with 13 on once daily regimen and 26 on bid regimen. Of these 39 patients the majority (82%) were male and the median age was 40 years. At baseline, the population enrolled did not suffer from critical deterioration of the immuno-virological status. Indeed, the median viral load was <4 log₁₀ copies/ml and the median CD4⁺ cell count was 312 cells/mm³. A significant proportion of patients had undetectable viral load (31%). There were also some patients who experienced early virological failure (>1000 copies/ml). Nevertheless, a significant proportion of patient was advanced in the disease progression (33% at CDC Stage C). In addition, although all patients had received prior PI therapy, 49% had received ≥ 3 prior PIs, 41% (16/39) were on a PI sparing regimen immediately prior to entry, receiving only NRTIs, NNRTIs or a combination of both. Of those subjects (n=23) who were receiving a PI regimen at screen, 74% (17/23) were on a RTV boosted regimen of which LPV/RTV was the most common (61%, 11/18).

The results at week 16 are presented in table 10.

Table 10: Study Outcomes at Week 16 for patients receiving fosamprenavir with ritonavir (MD=F)

OUTCOME	OD (N=13) n (%)	BID (N=26) n (%)	Total (N=39) n (%)
Responders <400 copies/ml plasma HIV-1 RNA	10 (77)	16 (62)	27 (69)
Virological failures	2 (15)	3 (12)	5 (13)
Premature discontinuation due to insufficient viral load response	0	1 (4)	1 (3)
Plasma HIV-1 RNA < 400 copies/ml	2 (15)	2 (8)	4 (10)
Premature discontinuations other than virological failure			
Adverse event	1 (8)	5 (19)	5 (13)
Other	0	3 (12)	3 (8)
Switch *	1 (8)	1 (4)	2 (5)
	0	1 (4)	0
Missing	0	2 (8)	2 (5)

* 1 subject was considered to be a premature discontinuation as switched from BID to OD group before Week 4. This subject is classed as a responder in the Total column.

The design of the study and the limited data weaken the findings of the study and therefore the use of fosamprenavir boosted with ritonavir in salvage therapy cannot be recommended before further data become available.

Clinical safety

- Patient exposure

The safety of fosamprenavir has been studied in over 1,000 patients including 755 patients in phase II and III controlled clinical trials. The safety of the co-administration of fosamprenavir with low dose ritonavir was established in study APV30002 (n = 322) in antiretroviral naïve patients, and in study APV30003 in protease inhibitor experienced patients, either once daily (1400 mg/200 mg) (n = 106) or twice daily (700 mg / 100 mg) (n = 106) regimen.

In APV30002/ APV30005, the median duration of exposure to fosamprenavir boosted OD population was 92 weeks. Globally twenty-three patients (11%) reported treatment emergent AEs leading to permanent discontinuation of treatment, in majority due to drug hypersensitivities all attributed to abacavir.

In study APV30003, at 48 weeks, 5 % of patients experienced premature treatment discontinuation due to adverse events, with a higher percentage in the lopinavir/ritonavir arm (8 %) than in the fosamprenavir boosted arms (2 % in the once daily regimen arm and 6 % in the twice daily regimen). The most common adverse event leading to permanent discontinuation of treatment were vomiting, which occurred with equal frequency across treatment groups, and nausea and dyspepsia which both occurred more frequently in the lopinavir/ritonavir group.

- Adverse events

Overall the safety of fosamprenavir is comparable to the one of amprenavir, which was expected because fosamprenavir is almost entirely metabolised to amprenavir before absorption.

Adverse events described with fosamprenavir are mainly related to gastrointestinal: diarrhoea, nausea, abdominal pain and vomiting.

In antiretroviral naïve patients (APV30002), the overall incidence of treatment-related grade 2-4 adverse events in the fosamprenavir boosted OD (41 %) was comparable to the nelfinavir (39%). However, the incidence in APV30002 was higher than the incidence with fosamprenavir with ritonavir OD group in APV30003 (22%).

As shown in table 11, more grades 2-4 gastro-intestinal events (mainly diarrhoea) were observed in treatment naïve patients than in treatment-experienced patients. Of note there was a slight higher use of anti-diarrhoeal compounds (24 % versus 18%) in experienced patients.

Table 11: MedRA Body Systems and most common treatment emergent-related Grade 2-4 Adverse Events occurring in patients receiving Fosamprenavir + ritonavir OD in APV30002 versus APV30003

	APV30002 (ART-naïve)	APV30003 (ART-experienced)
	Fosamprenavir + ritonavir OD N= 322 n (%)	Fosamprenavir + ritonavir OD N=106 n (%)
Body System		
Gastrointestinal Disorders	68 (21)	14 (13)
Metabolism and Nutrition	12 (4)	1 (<1)
Nervous System Disorders	18 (6)	2 (2)
Investigations	26 (8)	4(4)
Skin	23 (7)	3 (3)
Diarrhoea NOS	28 (9)	5 (5)
Nausea	21 (7)	4 (4)
Vomiting	19 (6)	3 (3)
Abdominal pain	8 (2)	4 (4)
Fatigue	11 (3)	4 (4)
Hypertriglyceridaemia	3 (<1)	0
Rash NOS	5 (2)	1 (<1)
Headache	8 (2)	0

In antiretroviral-experienced patients (study APV30003), the safety profile of the fosamprenavir boosted BID regimen was comparable with lopinavir/ritonavir BID.

When comparing the two regimens of fosamprenavir boosted with ritonavir, the overall incidence of drug related adverse events regardless of grade was similar in patients receiving the fosamprenavir boosted OD and fosamprenavir boosted BID regimens (51% and 55% respectively). However more patients in the fosamprenavir boosted BID group reported Grade 2-4 adverse events than with the once daily regimen (fosamprenavir boosted OD: 22% vs fosamprenavir boosted BID: 38% vs lopinavir/ritonavir BID: 37%). In particular there was a higher frequencies of treatment related Grade 2-4 AEs for gastrointestinal disorders, metabolism and nutrition disorders and nervous system disorders as displayed in table 12.

Table 12: Drug related Grade 2-4 AEs

	Fosamprenavir + ritonavir OD (%)	Fosamprenavir + ritonavir BID (%)
Body System		
Gastrointestinal Disorders	13 %	20 %
<i>Diarrhoea</i>	5%	11
Metabolism and Nutrition	< 1 %	7 %
<i>Hypertriglyceridemia</i>	0	4%
Nervous System Disorders	2 %	9 %
<i>Grade headache</i>	0 %	3%

Similar rates of drug related Grade 2-4 diarrhoea and Grade 2-4 headache to those seen in the BID group were observed in the lopinavir/ritonavir group. However, drug related Grade 1 to 4 diarrhoea was reported more often in the lopinavir/ritonavir group compared to the fosamprenavir boosted with ritonavir BID group (30% versus 23%, respectively).

Almost all cases of hypersensitivity reactions reported in phase III studies were attributable to abacavir. The incidence of hypersensitivity reactions in fosamprenavir groups and comparator groups was similar, as well as the severity. According to these data, the concomitant treatment of abacavir and fosamprenavir did not increase the risk of hypersensitivity reaction compared to the concomitant treatment of abacavir and another PI.

Laboratory abnormalities

In study APV30002/30005, median triglycerides, total cholesterol and LDL cholesterol levels did not appreciably change between Week 48 and Week 96. The median HDL cholesterol levels appeared to

increase continuously throughout the study period (median increase from baseline: from 8 mg/dl at Week 48 to 11 mg/dl at Week 96). Minimal absolute changes from baseline were observed in fasting glucose values. There was no apparent increase in lipodystrophy over a longer period of exposure (>48 to 96 weeks).

With regard to Grade 1 to 4 liver enzyme elevations there was no difference between fosamprenavir boosted OD group and nelfinavir group.

In study APV30003 there were no relevant differences in treatment-emergent grade 3/4 laboratory abnormalities between the fosamprenavir boosted BID and OD arms, except for Grade 3/4 triglyceride elevations (11 % versus 4%).

For fasting glucose, the median change from baseline over 48 weeks was slightly higher in the BID group compared to the OD group (change at week 48 7.2 mg/dl versus 1.8). There was no correlation between these events and plasma concentrations demonstrated except for fasting glucose elevations.

There was slightly higher number of patients in the fosamprenavir boosted arms that developed Grade 3/4 elevations in ALT and/or AST compared to the lopinavir/ritonavir group (6 % (6/106) in fosamprenavir boosted OD versus 6 % (6/106) in fosamprenavir boosted OD versus 4% (4/103) in lopinavir/ritonavir).

There was a higher incidence of Grade 3/4 serum lipase in the lopinavir/ritonavir group (12 %) than in the two regimens of fosamprenavir boosted (5 % in each arm).

Preliminary results of a study in healthy volunteers which aimed at exploring increased fosamprenavir and ritonavir doses to increase plasma amprenavir exposure showed that in 6 out of 42 subject there was a significant increase of liver transaminase (> 2.5 ULN in ALT and/or AST) especially in patients receiving 1400 mg BID boosted with ritonavir 200 mg BID. A warning has therefore been included in the Summary of Product Characteristics and the potential alteration of the safety profile of the combination with the use of doses of ritonavir higher than 100 mg BID.

- Serious adverse event/deaths/other significant events

The overall incidence of serious adverse events was low. In study 30003, a total of 37 patients experienced at least one treatment emergent serious adverse event irrespective of suspected causality during the study (fosamprenavir boosted OD: 15% (16/106) vs fosamprenavir boosted BID: 8% (9/106) vs lopinavir/ritonavir BID: 12% (12/103)).

The vast majority of these serious adverse events in trial APV30001 and APV30002 were drug hypersensitivity reactions attributed in almost all cases to abacavir. There was no death reported related to fosamprenavir.

- HBV/HCV co-infected patients and patients with liver impairment

A total of 269 HCV and/or HBV co-infected patients were included in the studies. The risk of treatment emergent Grade 3-4 liver function test elevations was greater in patients with hepatitis B and/or C co-infection at baseline in all treatment groups. In those patients entering the study with hepatitis B and/or hepatitis C co-infection there were no apparent differences between fosamprenavir and fosamprenavir boosted with ritonavir in the risk of liver function test elevations.

In study APV30002 and APV30003, a comparable but relatively low number of treatment naïve and treatment experienced patients (10 to 12%) had hepatic impairment (maximum grade 2 liver enzyme elevations) other than co-infection with hepatitis B and /or C at baseline. Treatment-naïve patients without hepatitis co-infection did not describe a specific risk to develop increases in hepatic enzymes, whatever baseline values. Treatment-experienced patients with pre-existing hepatic impairment described a higher risk to develop increases in transaminase values.

These results confirm that risk of liver impairment is increased in patients with elevated transaminase values or hepatitis co-infection at baseline.

- **Pregnancy**

Twelve pregnancies occurred in 11 patients exposed to fosamprenavir during pregnancy. Of these, 6 were aborted (2 spontaneous and 4 induced). Of the remaining 6 pregnancies, 5 went to term with no birth defects described and the outcome of 1 is unknown. The applicant undertook to provide outcome of pregnancies and to follow infants after birth during the post-marketing phase.

The safety of the recommended dose of the suspension compared to the coated tablets has not been investigated in clinical trials. It can be hypothesised that the presence of only small amounts of propylene glycol (10.2 mg/ml) in the suspension vs. the high amounts in the amprenavir oral solution already on the market (550 mg/ml) makes the fosamprenavir suspension a significantly safer product to deliver equivalent amounts of amprenavir to the patients.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The active substance is well characterised and documented. The pharmaceutical forms selected are adequate taking into account the properties and stability of the active substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing processes were developed and optimized to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the products are stable for the proposed shelf life. The unexpected bioequivalence findings related to processing and batch scale-up of the active substance and drug product (subsequently resolved) will have to be kept in mind when future changes are contemplated. A full and deep reassessment of quality will have to be considered at each change in manufacture process and batch size scale or any changes that could have an impact in-vivo applying for both drug substance and drug product.

Non-clinical pharmacology and toxicology

Fosamprenavir is the pro-drug of amprenavir, which is an inhibitor of the HIV protease, already on the market. Fosamprenavir has no or little antiviral activity *per se* and requires in-vivo metabolism to release the active moiety amprenavir. Amprenavir had previously been shown an antiviral activity both *in vitro* and *in vivo* against laboratory and clinical isolates compatible with a potential clinical use for the treatment of HIV infection. The general pharmacology studies showed no treatment related adverse effects.

The pharmacokinetics profile determined in mice, rats and dogs showed that fosamprenavir is rapidly absorbed after oral administration and extensively converted into amprenavir, widely distributed, and is eliminated primarily by hepatic clearance.

Overall, the toxicology programme showed that toxicity profile of fosamprenavir is similar to amprenavir. Treatment effects in the repeated dose toxicity studies included gastrointestinal intolerance. Liver was also the primary organ of toxicity. Fosamprenavir is not immunotoxic. There was no evidence of toxicity to reproduction. Fosamprenavir is not genotoxic. The lack of final results from the carcinogenicity studies was justified and in view of the benefit/risk ratio, the CPMP considered a marketing authorisation could be granted prior the availability of these results. However the applicant undertook to submit the final results as part of the follow-up measures to be fulfilled post-authorisation.

Efficacy

Fosamprenavir has been developed not only to optimise the use of amprenavir, by further reducing the pill burden but also to optimise/complete the clinical development of this compound in HIV infected naïve and pretreated patients.

The pharmacokinetics profile of fosamprenavir has been well defined and relevant information has been included in the Summary of Product Characteristics. Overall after oral administration, fosamprenavir is rapidly extensively converted to amprenavir prior to reaching systemic circulation. Ritonavir enhanced the pharmacokinetic parameters of amprenavir. Amprenavir is primarily eliminated via hepatic metabolism. Co-administration with compounds that interact with CYP450, P-gp or that affect fosamprenavir solubility may result in interaction. Additional data will be provided post-authorisation to complete the pharmacokinetic profile in particular with respect to interaction data and data in patients with hepatic impairment.

The dose of fosamprenavir was selected to provide comparable exposure to amprenavir. It was shown that similar plasma amprenavir pharmacokinetic parameter values were observed for equimolar fosamprenavir and amprenavir regimen (i.e amprenavir 600 mg bid and fosamprenavir 700 mg bid) and for equimolar fosamprenavir and amprenavir regimen boosted with 100 mg ritonavir bid.

In antiretroviral naïve patients, the efficacy of fosamprenavir boosted with ritonavir is based on one a single pivotal open label study versus nelfinavir. In this study fosamprenavir (1400 mg) given once daily with 200 mg ritonavir as part of a triple regimen including abacavir (300 mg bid) and lamivudine (150 mg bid) showed similar efficacy over 48 weeks compared to nelfinavir (1250 mg bid). The proportion of patients with HIV RNA below 400 copies/ml at week 48 was 69 % in the fosamprenavir arm versus 68 % in the nelfinavir arm. The virological failure was greater in the nelfinavir group (17 %) than in the fosamprenavir-boosted group (7%). In a roll-over study, 96 weeks non comparative data from patients treated with fosamprenavir/ritonavir OD were suggestive of a durable virological suppression.

In protease inhibitor experienced patients with virological failure (less than or equal to two PIs), the efficacy of fosamprenavir boosted with ritonavir (either 700 mg + 100 mg bid or 1400 mg + 200 mg OD) was compared in a randomised open-label study to lopinavir/ritonavir. At 24 weeks, the non-inferiority could be concluded between the treatments with regard to virological suppression as measured by the average area under the curve minus baseline for plasma HIV-RNA, even if the point estimates were always in favour of the lopinavir/ritonavir arm. The difference in favour of lopinavir/ritonavir was statistically significant in the subgroup of patients with high viral load at baseline (>100 000 copies/ml)

The fact that Telzir associated with ritonavir was not shown to be non-inferior to lopinavir/ritonavir at 48 weeks has been reflected in the Summary of Product Characteristics and the applicant undertook to explore an intensification of treatment in patients failing to achieve adequate virological suppression with fosamprenavir boosted.

Similarly when considering the proportion of patients with viral load below the limit of detection, (secondary endpoint), results were far from the demonstration of non-inferiority between the treatments, although the study was not sufficiently powered for this assessment, conversely to the assessment of primary endpoint, AAUCMB at 24 and 48 weeks. The suggestion of a superiority of lopinavir/ritonavir is even more noticeable in the difficult-to-treat population with high viral load at baseline (>100 000 copies/ml). The results were even more critical when considering the once daily regimen.

In term of resistance, overall the addition of ritonavir, as pharmacokinetic enhancer, to fosamprenavir led to reduction in the development of resistance in antiretroviral naïve patients. The occurrence of PRO mutations was 0 % in study APV30002 *versus* 17 % in APV30001 where fosamprenavir was given unboosted. RT mutations in NRTI were also significantly reduced (13% versus 55%). The amprenavir-associated resistance mutations that emerged in study APV30001 with fosamprenavir non boosted with ritonavir were consistent with primary mutations described in patients treated with amprenavir.

In the antiretroviral experienced population, viruses that have developed resistance as a result of prior PI therapy are more likely to remain susceptible to amprenavir and lopinavir, than to other PIs.

A deleterious impact of the presence of 4 or more mutations among the following ones: L10F/I/V, K20R/M, E35D, R41K, I54V, L63P, V82A/S/T/F and I84V to response (<400 copies/ml at Week 48) to 908/RTV has been shown and is important to take into account in the therapeutic management of patients.

The applicant undertook to perform genotypic and phenotypic analyses in ongoing and planned studies with correlation with pharmacokinetic exposure and virological response.

Cross-resistance to amprenavir or other protease inhibitors does not appear to develop in previously treatment naïve subjects failing a boosted fosamprenavir regimen.

There are currently insufficient data in heavily pre-treated antiretroviral experienced patients to recommend the use of fosamprenavir in deep salvage therapy.

There is currently no efficacy and safety data in children, but the applicant undertook to submit the results of ongoing paediatric studies using the oral solution as part of the follow-up measures to be fulfilled post-authorisation.

Safety

The safety profile of fosamprenavir with ritonavir was evaluated in combination with various other antiretroviral agents. No new safety issues have emerged with the prodrug compared to the amprenavir. Adverse events relate mainly to gastro-intestinal disorders, particularly diarrhoea. Safety profile in naïve patients was generally comparable in term of types and incidences of adverse events to the ones observed in treatment experienced patients. Safety profile of fosamprenavir boosted BID was comparable to lopinavir/ritonavir. Although liver was the target organ in the preclinical studies, there was no sign in the clinical studies of liver toxicity associated with fosamprenavir.

The class labelling on the adverse events which have been associated with the use of antiretroviral therapies such as lipodystrophy, metabolic abnormalities, hyperglycaemia, or with protease inhibitors such as rhabdomyolysis and spontaneous bleeding in haemophiliac patients have been included in the Summary of Product Characteristics.

The following events will also be monitored during the post-authorisation phase: gastro-intestinal events (diarrhoea), headache, glucose and lipids abnormalities (hypertriglyceridemia), hypersensitivity and skin events, transaminase elevations and cardiac events.

Benefit/risk assessment

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

In antiretroviral naïve patients, the CPMP considered that the efficacy demonstration was acceptable although not optimal, especially in the absence of bridging studies with amprenavir in this population. In addition the demonstration was only supported by one single open label study versus nelfinavir. However nelfinavir was the most prescribed protease inhibitor at the time of the initiation of the study and lopinavir/ritonavir, which has become a preferred used protease inhibitor in this population, was not yet authorised. The CPMP concluded that an approval for fosamprenavir/ritonavir BID could only be considered in this population provided that:

- the same schedule regimen as in antiretroviral experienced patients, i.e. a BID regimen (allowing to achieve 20-30 % increased C_{min} , which minimise the risk of sub-optimal concentrations) was recommended, as a conservative measure.
- the applicant performs a clinical study in antiretroviral naïve patients versus lopinavir/ritonavir, to help physicians in determining the optimal therapeutic strategy in clinical practice. The applicant undertook to conduct this study, the results of which would be submitted as part of the follow-up measures to be fulfilled post-authorisation.

In antiretroviral experienced patients, the efficacy demonstration was far less convincing. Indeed in the pivotal study APV30003 enrolling moderately antiretroviral experienced patients, 48 week results

were not compatible with a demonstration of non-inferiority between fosamprenavir boosted with ritonavir and lopinavir/ritonavir. The suggestion of a superiority of lopinavir/ritonavir was even more noticeable in the difficult-to-treat population with high viral load at baseline (>100 000 copies/ml). These considerations applied for both fosamprenavir boosted with ritonavir once daily and twice daily regimens, but were even more critical for the once daily regimen. In relation with the lower virological suppression achieved with fosamprenavir with ritonavir in comparison to lopinavir/ritonavir a higher emergence of resistance was observed.

However, CPMP considered that the comparison with lopinavir/ritonavir should not preclude an approval in antiretroviral-experienced patients considering that:

- fosamprenavir is the prodrug of amprenavir already approved in this specific population and can be regarded as an optimisation of amprenavir
- there is no argument in favour of a deterioration of the benefit/risk ratio of the prodrug in comparison to the amprenavir.
- this prodrug presents the potential advantage of an improved compliance by the reduction of the pill burden which may be added value of particular importance in this population.
- the clinical experience gained with the prodrug and the amprenavir (the pharmacokinetic direct comparison with the amprenavir and fosamprenavir allows to bridge the clinical experience of both drugs) allowed to substantiate the efficacy and safety profiles of fosamprenavir.

The failure to establish non-inferiority has however been clearly reflected in the Summary of Product Characteristics and the applicant undertook to explore an intensification of treatment in patients failing to achieve adequate virological suppression with fosamprenavir boosted.

There are however insufficient data to recommend the use of fosamprenavir with ritonavir in heavily pre-treated patients.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Telzir was favourable and therefore recommended the granting of the marketing authorisation in the following indication:

“Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products.

In moderately antiretroviral experienced patients, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir.

In heavily pretreated patients the use of Telzir in combination with low dose ritonavir has not been sufficiently studied.

In protease inhibitor (PI) experienced patients the choice of Telzir should be based on individual viral resistance testing and treatment history”.