SCIENTIFIC DISCUSSION

1. Introduction

The World Health Organisation (WHO) estimated that there were at least 40 million people worldwide with Human Immunodeficiency virus (HIV) infection in 2004, and that 6 million needed treatment.

Current treatment options consist of four different mechanistic classes of compounds:

- NRTIs (nucleoside/nucleotide reverse transcriptase inhibitors) inhibiting the reverse transcriptase (RT) of HIV by structural similarity with the substrate of RT.
- NNRTIs (non-nucleoside reverse transcriptase inhibitors) inhibiting the reverse transcriptase of HIV without being nucleosides analogues.
- PIs (protease inhibitors) inhibiting the HIV protease which is an enzyme required for the assembly and release of mature HIV particles from the cell after the replication cycle.
- Entry inhibitors: only one representative of fusion inhibitors, which inhibits fusion of the HIV with CD4+ cells, thus infection of cells is currently approved (enfuvirtide).

Medicinal products containing one or more of these agents are required for building combination antiretroviral therapies (CARTs). 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 their therapy.

APTIVUS which contains tipranavir, a non-peptidic protease inhibitor has been developed for treatment-experienced patients who have HIV-1 strains with PI resistance associated mutations (PRAMs). A so-called stand alone application has been submitted for registration. APTIVUS is available as 250 mg soft capsules. The recommended dose is 500 mg to be co-administered with low dose of ritonavir (200 mg as pharmacokinetic enhancer) twice daily.

The approved indication is:

> "APTIVUS, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.
> This indication is based on the results of two phase III studies, performed in highly pre-treated patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors (see details of resistance profile of patients' HIV at baseline in section 5.1 *of the Summary of Product Characteristics*).
> In deciding to initiate treatment with APTIVUS, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of APTIVUS."

2. Quality aspects

Introduction

APTIVUS is presented in the form of gelatine soft capsules containing 250 mg of tipranavir as active substance. Other ingredients are macrogolglycerol ricinoleate, ethanol, mono/diglycerides of caprylic/capric acid, propylene glycol, purified water, trometamol, propyl gallate, gelatine, red iron oxide, titanium dioxide, sorbitol special-glycerin blend (d-sorbitol, 1,4 sorbitan, mannitol and glycerin) and black printing ink.
The capsules are packed in HDPE bottles with child resistant closure.

Active Substance

Tipranavir which has the chemical name N-[3-[(1R)-1-[(5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide is a white to off-white to slightly yellow poorly crystalline solid. Its solubility in water is very low and pH dependent but it is highly soluble in various organic solvents and surfactants.

The chemical structure of tipranavir is well characterised. The absolute stereochemistry of tipranavir has been determined and the configuration of the stereocenters was confirmed to be 1R, 6R.
Tipranavir is a poorly crystalline substance. A single polymorphic form of tipranavir has been used for all development work and is the proposed commercial form of the drug substance.

- Manufacture

The commercial process is carried out using a three-step synthesis starting from three key starting materials.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- Specification

The active substance specification includes tests for appearance, clarity of solution, colour of solution, identification (IR, HPLC), assay (HPLC, 98.0-102.0%), impurities (HPLC), stereoisomeric impurities (CE), residual solvents (GC), organic volatile impurities (GC), water content, sulphated ash, heavy metals, sulphate content.
The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.

Batch analysis data of a number of batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

Stability studies were conducted according to ICH conditions. Three full scale production batches were stored for 24 months under long-term storage conditions (25°C/60% RH), 12 months at intermediate conditions (30°C/70% RH) and for 6 months under accelerated conditions (40°C/75% RH). The stability samples were packaged in a container closure system that mimics the one which will be used for the commercial drug substance. The parameters tested were appearance, clarity of the solution, colour of the solution, identification (IR, HPLC), assay (HPLC), impurities (HPLC), stereoisomeric impurities (CE), water content, X-Ray powder diffraction.

Tipranavir was also exposed to various stress conditions, *i.e.* exposure in the solid state to elevated temperature under both uncontrolled humidity and high humidity, and to light irradiation; exposure in aqueous solution to elevated temperature and different pH values, and to strongly oxidizing conditions. The parameters tested were impurities (HPLC) and assay (HPLC).

The proposed retest period and storage conditions are justified based on the stability results.

Finished Product

- Pharmaceutical Development

The physicochemical and biopharmaceutical properties of tipranavir, coupled with the clinical requirement of a high dose (1000 mg per day), precluded the development of a conventional dosage

form. A self-emulsifying drug delivery system (SEDDS) in a soft gelatin capsule was chosen for development to overcome the dissolution rate limited absorption of the tipranavir drug substance, since the drug is dissolved in the SEDDS vehicle. Other approaches were also evaluated early in development, but these approaches were inferior to the SEDDS formulation in terms of *in vivo* performance. Upon exposure to the gastro-intestinal tract the drug product capsule shell dissolves, thus exposing the fill material to the aqueous gastro-intestinal environment. The components of the fill material spontaneously emulsify upon exposure to water.

An oral solution was developed to be used in children and in adults who could not swallow the capsules. The bioequivalence between the capsule and oral solution was not demonstrated. The CHMP considered therefore that there was a need to substantiate the interchangeability of the capsule and the oral solution to enable proper dosing recommendations, and to ensure adequate efficacy and safety of this pharmaceutical form before a marketing authorisation for this pharmaceutical form could be granted.

The selection of excipients and their corresponding levels was based on *in vitro* dispersion, stability, and *in vivo* bioavailability studies using various prototype SEDDS formulations. The selection and optimization of individual components of the proposed commercial formulation were discussed in detail. The chosen excipients in the capsule fill solution are: ethanol, propylene glycol, macrogolglycerol ricinoleate, mono/diglycerides of caprylic/capric acid, trometamol, purified water, and propyl gallate. The excipients in the capsule shell are: gelatine, red iron oxide (E172), propylene glycol, purified water, 'Sorbitol special-glycerin blend' (D-sorbitol, 1,4 sorbitan, mannitol and glycerin) and titanium dioxide (E 171) and black printing ink.
All of the excipients in the capsule fill solution except mono/diglycerides of caprylic/capric acid are compendial excipients controlled according to the current monograph in the Ph.Eur.

The composition of the finished product used in clinical studies is identical to that proposed for marketing with the exception of the imprinting of the capsule shell.

TSE certificate of suitability for gelatin included in capsule shell was provided.

Tipranavir capsules are packaged in HDPE bottles, with a plastic child resistant closure and an induction foil seal. Specifications and analytical procedures to control the components of the container closure system submitted are satisfactory.

- Manufacture of the Product

The manufacturing process includes three major operations: manufacture of bulk fill solution, manufacture of the gel mass, and manufacture of the finished capsules.

The manufacturing process has been adequately validated by a number of studies for the major steps of the manufacturing process in three commercial batches.

The batch analysis data show that the soft capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The release specification includes tests by validated methods for description of the capsule shell, description of capsule fill, identification (HPLC, UV), assay (HPLC, 95.0%-105.0% claim), degradation products (HPLC), dissolution (Ph Eur), uniformity of dosage units (HPLC), water content of capsule fill, propyl gallate content of capsule fill (HPLC), trometamol content of capsule fill (HPLC), microbial limits (Ph.Eur), identification of propyl gallate (HPLC), identification of titanium dioxide (Ph Eur) and identification of iron oxide.

The test and limits of the release and shelf life specification for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.

Batch data are provided for pilot and production batches and indicate satisfactory uniformity as well as compliance with the specification.

- Stability of the Product

Stability data are available for 6 primary stability batches (clinical batches) stored at the 4°C/NR RH up to 36 months for the first batch, up to 24 months for the second and third batches and up to 18 months for the last three batches. For the accelerated condition 25°C/60%RH stability data are available up to 6 months for all six batches.
The following parameters were tested: description of capsule shell, description of capsule fill, assay (HPLC, 92.0-105.0%), degradation products, dissolution, water content, propyl gallate content, trometamol content, ethanol content, propylene glycol content and microbial limits.

The finished product showed to be physically and chemically stable under the refrigerated conditions. On the basis of the stability data available, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

3. Non-clinical aspects

Introduction

Tipranavir (TPV) is non-peptidic HIV protease inhibitor belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. It has anti-viral activity against HIV-1 and HIV-2.
The preclinical programme consisted on a wide range of studies conducted with TPV. In order to improve its bioavailability, it was decided to co-administer TPV with low dose of ritonavir (RTV), a so-called boosting regimen. In this regard, additional non-clinical studies have been conducted to investigate pharmacokinetics and toxicology of TPV co-administered with low dose RTV. To further improve the bioavailability and tolerability of TPV, a soft gelatin capsule SEDDS (self-emulsifying drug delivery system) formulation was developed. The pharmacokinetics and potential toxicity of this formulation has been addressed in additional non-clinical studies.

Pharmacology

- Primary pharmacodynamics

Inhibition of HIV protease in vitro

In enzymatic assays, TPV demonstrated potent and selective inhibition of the cleavage of a peptidic substrate by HIV-1 protease with an inhibition constant (Ki) of 8.9 ± 6.8 pM. It was also active against HIV-2 protease (Ki <1nM).

Selectivity of TPV for the HIV protease was demonstrated by high Ki values against the human aspertyl proteases pepsin, cathepsin D and cathepsin E (Ki=2, 15 and 9 µM, respectively).

Antiviral activity in vitro

The antiviral activity of TPV was assessed in several cell cultures systems and HIV-1 strains. Using laboratory strains of HIV and T-lymphocytic cell lines, EC_{50} values ranged from 0.03 to 0.07µM (18 to 42 ng/ml) and EC_{90} values ranged from 0.07 to 0.18µM (42 to 108ng/ml). An average EC50 of 0.07µM (42ng/ml) was obtained against 10 randomly selected clinical isolates replicating in primary blood mononuclear cells (PBMCs).
These active concentrations were below the cellular toxicity concentration range of 7-35 µM demonstrated for TPV in a number of cell lines.

TPV is highly bound to proteins (99.88%) when present in the cell culture medium and 99.97% bound to proteins when present in whole human plasma. However, the addition of up to 75% human plasma

to the cell culture medium resulted only in a 3.75-fold shift (mean value) in antiviral activity compared to conditions where no human serum was added. Therefore, the high level of protein binding is not expected to limit the *in vivo* antiviral activity of TPV. According to these data, the concentration needed to inhibit HIV replication in human blood would be approximately 3.75-fold higher than the concentration observed to inhibit HIV replication in cell culture, and would range in EC_{90} from 0.26 to 0.68µM (157ng/ml –410ng/ml) for most clinical isolates.

- Secondary pharmacodynamics

TPV was evaluated for effects on immune function in mice, and slight (25 %) to modest (39 %) effects on T-cell activation were observed at an oral dose of 300 mg/kg oral dose.

In an in vitro receptor-binding screen against a variety of receptor targets, TPV displayed a relatively low inhibitory profile against the majority of receptors. One exception is the CCK-A (cholecystokinin-A) receptor, a peptide known to be involved in the food digestion in the gastroinstestinal tract, where TPV was shown to bind with modest affinity of 27% at 0.1 µm and 82% at 10 µM. Furthermore, TPV also inhibited the CL channel (picrotoxin) at 10 µM by 89 %.

- Safety pharmacology

In a series of in vitro and in vivo safety pharmacology studies assessing effects on a number of organ systems, including cardiovascular, central nervous, pulmonary, renal and gastrointestinal, TPV showed no effect on the majority of organ functions. In renal studies in rats, TPV administered with doses up to 625 mg/kg for males and 500 mg/kg for females, elicited significant decreases in K+ excretion and significant increases in Na+ excretion. In a study in rats assessing the gastrointestinal function at the same doses, TPV inhibited gastric emptying, significantly decreased gastrointestinal propulsion, increased gastric fluid volume and decreased fluid acid concentration dose-dependently.

TPV inhibited HERG channel current in a dose dependent manner with an IC_{50} of 2.9µM. There was no effect observed in the test in guinea pig papillary muscle tissue using doses up to 10 µM. Similarly there were no significant effects on QT prolongation observed in in vivo conscious dog ECG studies. All these results suggest that TPV may have little to no pro-arrhythmic effects.

- Pharmacodynamic drug interactions

Because TPV will be administered to HIV infected patients as part of a CART regimen, the activity of TPV in combination with other anti-HIV agents was determined in vitro in culture. Synergy to additivity was observed between TPV and zidovudine, whereas synergy was observed between TPV and ritonavir. For the PIs amprenavir and lopinavir conflicting results of additivity and antagonism were observed.

Pharmacokinetics

The pharmacokinetics of TPV were investigated following single and/or repeated dosing in mice, rats, dogs, rabbits and monkeys, using in most of the studies a basified aqueous solution. Because in clinical practice tipranavir is to be boosted with a low dose of ritonavir, the pharmacokinetics of tipranavir co-administered with RTV, was also investigated in mice, rats, dogs and monkeys.

- Absorption

Following intravenous dosing, TPV demonstrated low clearance ranging from 0.08 l/h/kg in dogs to 1.15 l/h/kg in mice. The Vss ranged from 0.13 l/kg in dogs to 0.51 l/kg in rats. TPV was eliminated rapidly with a terminal $t_{1/2}$ ranging from 0.93 h in dogs to 5.43 h in rats. Following oral dosing, TPV exhibited a mean Tmax ranging from 0.5 to 8 h in all species. In all species a moderate or poor oral bioavailability of TPV was revealed, due to a lack of absorption and/or intestinal metabolism. Whereas the bioavailability in rats showed moderately levels of 28.0%, the bioavailability in dogs (6.5% and 7.7%) and also in mice (11%) and rabbits (9.9%) was minimal. Food had no significant

effect on TPV oral bioavailability in dogs. Ritonavir co-administration studies were performed to investigate the benefit gained by the combination. However the use of different doses of ritonavir for oral and intravenous PK of tipranavir does not allow a clear comparison of tipranavir bioavailability with or without ritonavir.

With RTV co-administration, following intravenous dosing, TPV demonstrated low to moderate clearance ranging from 0.0182 l/h/kg in rats to 3.00 l/h/kg in mice. In rats and dogs, co-administration of RTV resulted in a 4- to 5-fold decrease in clearance for TPV, which would be consistent with inhibition of drug-metabolising enzymes by RTV.

Following repeated daily dosing of TPV alone, the increase in TPV exposure was less than proportional to dose and exposure declined in mouse (90 to 99%), rat (30 to 90%), dog, and monkey (50 to 75 %). The decline may be attributed to enzyme induction by TPV which was observed in rats and dogs.

Co-administration of RTV increased TPV exposure on day 1 and following repeated dosing. In the rat, the RTV co-administration induced an increased of tipranavir bioavailability from 28 to 58.7 %. In the dog no clear conclusion could be draw.

Regarding the absorption, sex differences were noted in mouse and rat studies with greater exposure in females compared to males.

- Distribution

The *in vitro* plasma protein binding of TPV was very high (> 99.9%) in all species including humans, with only a slight trend towards saturation over the concentration range of 10 to 100 µm.
TPV with or without RTV co-administration, distributed primarily in the liver, small intestine, large intestine, kidney and lung. TPV did not cross the blood-brain barrier and did not readily partitioning into red blood cells.

TPV oral bioavailability was similar in both pregnant (10.7%) and non-pregnant rabbits (9.9%). In lactating rats TPV alone or co-administered with RTV was secreted in milk. TPV also crossed the placenta of pregnant rats. It did not readily cross the blood brain barrier in both pregnant rats and foetus.

- Metabolism

The metabolism of TPV, in the absence of ritonavir was assessed *in vitro* with hepatic microsomes of rat, dog, monkey and human and with hepatocytes. This study demonstrated that the metabolite profile was qualitatively similar between species. A number of metabolites were generated which included several mono-hydroxylated metabolites, a glucuronide conjugate of the parent, desaturated metabolites, and a cleavage product formed via N-S bond cleavage.

Plasma samples from rat, dog, monkey and human dosed orally by TPV were analysed for the presence of metabolites. Two primary metabolites (M3 and M4), suggested to be formed by intramolecular cyclization of TPV, were identified. Two additional metabolites (M1 and M2) were identified as further oxidation products of M3 and M4, respectively. They were only found in monkey and human plasma, but not in rat and dog plasma.

Furthermore, studies in rats and humans dosed by TPV co-administered with RTV were conducted to assess metabolites. The unchanged TPV was the predominant form in plasma (>85.7%). Unchanged TPV was also the major form excreted in faeces and urine. Combined levels of excreted metabolites in faeces and urine accounted for approximately 4.8% and 7.4% in male and female rats. Only small amounts of a glucuronide were observed in faeces.

In vitro metabolism studies indicated that CYP3A4 is the predominant CYP isoform involved in TPV metabolism in humans. CYP3A isozyme was also identified in rat as the predominant CYP isoform involved in TPV metabolism.

Induction of isoforms of CYP450 was investigated in rats and dogs which showed an increase in liver weight and in the total P450 content as well as an induction of CYP3A and 2B isozymes in rats and of CYP3A12 and 2B11 isozymes in dogs.

TPV is a substrate of Pgp which can be inhibited by RTV co-administration. Studies assessing whether tipranavir is an inhibitor or inducer of this transporter are in progress, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

In all tested species, excretion of TPV occurs primarily via bile into the faeces with greater than 87% of an administered dose excreted into faeces in mice, greater than 75% in rats, greater than 82% in rabbits, and greater than 68% in dogs. Enterohepatic recirculation of radioactivity was also observed in rats.

Toxicology

A complete toxicological programme has been performed with tipranavir. It included single dose studies (mice, rats and dogs), repeated dose studies (tipranavir alone in mice, rats and dogs and tipranavir + ritonavir in rats and dogs), genotoxicity and reproductive and developmental toxicity studies (rats and rabbits). Carcinogenicity studies with tipranavir and tipranavir + ritonavir are ongoing in rats and mice.
TPV was administered in toxicity studies as either the free acid or the disodium salt. In this report all doses administered to animals and the calculated effect levels are expressed as free acid equivalents.

- Single dose toxicity

In non Good Laboratory Practices (GLP) single dose oral toxicity studies in mice, rats and dogs the approximate minimum lethal dose of TPV was 3000 mg/kg in mice, 2330 mg/kg in male rats and 1500 mg/kg in female rats and >500 mg/kg in dogs. Common findings among the species tested were gastrointestinal symptoms including emesis, soft stools and/or diarrhoea. In rats, slight elevations of coagulation parameter were noted in females. Despite the non-compliance to GLP, the CHMP considered that the need to repeat the studies was superseded by the data from the repeated dose toxicity and the clinical experience.

- Repeat-dose toxicity studies

Repeat-dose toxicity of TPV has been addressed in mice up to 13 weeks with oral doses up to 360 mg/kg/day, in rats up to 26 weeks with doses up to 400 mg/kg/day and in dogs up to 39 weeks with doses up to 320 mg/kg/day. In addition repeat-dose toxicity of TPV co-administered with RTV has been performed in rats and dogs in studies up to 26 weeks of duration (with doses up to 1200 mg/320 mg tipranavir/ritonavir).

Effects of TPV in repeat-dose toxicity studies with TPV were observed primarily in the liver, the gastrointestinal tract, the coagulation system and the testes. Additional organs that were affected included the thyroid gland and to a lesser extent, the adrenal gland, kidneys, spleen, and heart. In studies on TPV with RTV co-administration revealed only signs of toxicity or target organ effects evident when each compound was administered alone and did not exacerbate the toxicity of either compounds.

Effects on the gastrointestinal system

These included emesis, soft stools, diarrhoea, and/or excessive salivation and were observed in all species tested. These GI effects have been judged to reflect local actions as no correlative macroscopic or microscopic changes in the GI tract were observed in mice, rats, or dogs. Addition of RTV to TPV

dosage regimens was without effect on either the incidence or severity of GI effects in rats and dogs. These effects resolved spontaneously or disappeared with cessation of TPV administration. In the rat, NOAEL were 20 mg/kg for females and 40 mg/kg for males in the 26-week study, which correspond to 0.1 fold the human exposure. In the 39-week study dog, no NOAEL could be established.

Effects on the liver

Liver is a target organ of TPV in all species tested: rats, mice and dogs. Hepatic effects of TPV common to all species included increased liver weights and hepatocellular hypertrophy.
Changes specific to rodents and noted at higher dose levels included evidence of hepatocellular degeneration as well as vacuolation, necrosis, and mineral deposition in mice and multinucleated hepatocytes in rats. These findings were not considered as direct effects of TPV on the liver. Karyomegaly was observed at a low incidence in rats in all TPV/RTV co-administration groups for 26 weeks. Histologic changes specific to dogs included bile duct hyperplasia after TPV administration, and gallbladder cystic hyperplasia. This effect was not noted in dogs co-administered TPV and RTV. Hepatic effects of TPV were partly reversible.

Beagle dogs exposed to TPV or TPV/RTV displayed mild increases in alkaline phosphatase (AP) at high dose levels. There were no other signs of more severe histopathology (biliary stasis, increased GGT and bilirubin). In contrast, rats exhibited decreased serum AP at higher dose levels in a number of studies. Increases in AST and/or ALT were observed minimally or not at all in toxicity studies on rats and beagle dogs.

Most of the hepatic effects noted in the liver in rodents could be considered secondary to hepatic enzyme induction. Nonetheless, hepatic effects were observed in all studies, in all species and the majority of these effects appeared at exposure levels which are equivalent to of below the human exposure and safety margins could not be established.

Effects on the testes

Testicular effects consisting of decreased weights and bilateral seminiferous tubule degeneration and/or atrophy were observed in a 26-week TPV/RTV study in rats at a dose level of 1200/320 mg/kg/day TPV/RTV and in the 39-week study in dogs after administration of 320 mg/kg/day TPV alone. Further review of these findings led to the conclusion that the testicular effects were not attributable to tipranavir.

Effects on the thyroid gland

Increased thyroid gland weights as well as thyroid follicular hypertrophy were noted regularly in 2 to 26 week studies performed in rats. In general, increases in thyroid stimulating hormone (TSH) as well as decreases in triiodothyronine (T3) and thyroxine (T4) were observed, but this was not consistent in all studies at all time points measured. Thyroid gland changes in TPV-dosed rodents are considered to reflect a rodent specific increase in thyroid hormone metabolism secondary to induction of hepatic drug metabolising enzymes.

Additional organ effects

Adrenal gland effects consisted of increased adrenal weights without correlative microscopic changes, with the exception of one 4-week study in mice where hypertrophy of the zona fasciculata was observed at the highest TPV and TPV/RTV dose levels. Based on the high dose levels that caused these findings, the minimal to mild effects noted, and the lack of biologically relevant changes in dogs, the effects on the adrenal gland in rodents were attributed to stress, and not to a direct effect of TPV.

Changes in the kidneys consisted of an increased urinary protein and exacerbation of chronic progressive nephropathy (CPN), a rodent specific spontaneous change, in a 26-week rat study. This was accompanied by proteinuria and increased kidney weight. Systemic exposure was lower than therapeutic exposure in humans**.** Kidney changes were not noted in any other species, nor in the 26-

week TPV/RTV in rats. This increased incidence was therefore considered as an exacerbation of CPN and does not represent an underlying renal toxicity caused by tipranavir administration.

Increased extramedullary haematopoiesis was observed in the spleen in mice, rats, and dogs. This finding was judged secondary to the mildly reduced red blood cell parameters in rats and dogs, and haemorrhage observed in the 26-week TPV/RTV rat study.

Minimal to mild myocardial degeneration was observed in one study in mice when TPV was administered by diet over 13 weeks. No heart changes were observed in any gavage administration study in mice up to 13-weeks, nor have heart changes been seen in any study in rats or dogs. Consequently, the significance of this finding in relation to humans is unclear.

Lymphocytolysis was also observed. An immunotoxicity study has been conducted in mice treated for 28 days to TPV/RTV the highest dose being 300/80 mg/kg. TPV/RTV had no effect on the antibody response following immunisation with a T-cell dependent antigen.

Effects on coagulation

TPV increased coagulation parameters (i.e., prothrombin time and activated partial thromboplastin time) in rats, mainly in males and provoked excessive haemorrhages. No increase in coagulation parameters was observed in studies in beagle dogs. Given that TPV was synthesised on the structural basis of coumarin-like anticoagulant agents, the possibility of an interference with vitamin K metabolism cannot be ruled out. Further mechanistic study will be conducted to elucidate the mechanism of action of the anticoagulant effect of TPV, the results of which would be provided as part of the follow-measures to be fulfilled post-authorisation.

- Genotoxicity/carcinogenicity

TPV was neither mutagenic nor clastogenic in a battery of in vitro assays (bacterial reverse mutation assay, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes) as well as an *in vivo* micronucleus assay in mice with oral dose up to 2600 mg/kg/day. Due to the lack of toxicokinetics data, two additional micronucleus studies were conducted in rats at oral doses up to 1200 mg/kg/day which led to exposure comparable to the one obtained in humans confirming the absence of clastogenicity.

Two-year carcinogenicity studies in mice and rats with TPV are ongoing. Considering that tipranavir is intended for heavily pre-treated HIV patients, for whom there is an unmet medical need, the CHMP 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.

- Reproductive and developmental studies

The reproductive effects of TPV were assessed in standard tests in rats and rabbits. In rats doses of 40, 400 and 1000 mg/kg/day were administered orally. In the embryotoxicity study in rabbits doses of 75, 150 and 375 mg/kg/d were used. All doses were divided into two equal doses given 8 hours apart.
Treatment with TPV did not affect reproductive capacity nor performance in rats at any of the doses tested.
Except for hepatomegaly and/or increased liver weights which already occurred at the lowest dose tested, maternal toxic effects were restricted to medium and high dose groups in rats and high dose group in rabbits. A NOAEL for developmental toxicity has not been established, as skeletal malformations were observed in the offspring of all treatment groups in the rabbit study and an increased mortality and delay in reflex development occurred in the prenatal and postnatal study in rats in all treatment groups, as well. Furthermore, gross and visceral malformations were also observed in high dose group foetuses in the rabbit study and visceral malformations in the medium and high dose groups in rats. Because these effects occurred at exposure levels below human exposure levels at

the recommended dose level, these malformations were further assessed and it was concluded that tipranavir did not have any teratogenicity potential.

In the prenatal and postnatal development studies in rats, mean pup weight was reduced significantly at the high dose at the end of lactation.

No studies in juvenile animals had been conducted.

- Local tolerance

Local irritation studies in rabbits indicated that TPV powder was minimally irritating to the eye and mildly irritating to abraded skin with open wounds.

- Other toxicity studies

Impurities present in the proposed acceptance criteria for TPV drug substance and drug product were qualified in toxicity studies investigating repeat-dose toxicity, mutagenicity, and clastogenicity. No toxicity signs specific to the presence of impurities was observed in these studies.

Studies in rats and dogs with the SEDDS bulk fill solution revealed no specific safety concerns for use of tipranavir capsules in humans.

- **Ecotoxicity/environmental risk assessment**

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

4. Clinical aspects

Introduction

The clinical programme consisted of:

- studies aiming to characterise the pharmacokinetic profile of tipranavir following single and multiple administration with or without ritonavir;

- three phase II dose ranging studies in treatment experienced patients;

- two open-label, pivotal active-controlled Phase III studies in triple antiretroviral (ARV) class experienced patients: RESIST –1 (1182.12) and RESIST-2 (1182.48);

- one supportive Phase II study (1182.51) conducted in triple ARV class, dual PI regimen-experienced and multi-PI resistant patients who failed to entry in RESIST studies;

- one Phase I/IIa paediatric study (1182.14) performed with a TPV oral solution in children from 2 to 18 years of age;

- one rollover long term safety study (1182.17) for TPV-treated patients from all trials and comparator PI failure patients from RESIST 1 and RESIST 2

The applicant claimed that all studies were performed according to Good Clinical Practices. The design of the pivotal studies has been discussed in the context of a Scientific Advice.

At the recommended dose of 500 mg to be co-administered with low dose of ritonavir (200 mg as pharmacokinetic enhancer) twice daily, the approved indication is:

"APTIVUS, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.
This indication is based on the results of two phase III studies, performed in highly pre-treated patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors (see details of resistance profile of patients' HIV at baseline in section 5.1 *of the Summary of Product Characteristics*).
In deciding to initiate treatment with APTIVUS, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of APTIVUS."

Pharmacokinetics

The pharmacokinetics profile of tipranavir was determined in a series of studies including in total approximately 650 HIV-negative subjects and approximately 665 HIV-positive patients (including 33 paediatric patients).
In addition, a population PK study was submitted, pooling the data from 6 studies (2 in HIV-positive patients and 4 HIV-negative subjects).
Except for one study on the relative bioavailability of the oral solution, all studies investigating the pharmacokinetics of TPV co-administered with RTV were performed using the early capsule or the final SEDDS capsule formulation.
The analytical methods used have been adequately validated.

- Absorption

Because TPV has a low solubility, no quantification of absolute absorption is available. Due to the lack of an adequate intravenous formulation, the absolute bioavailability of TPV could not be investigated.

TPV alone: The PK of TPV alone was investigated in early pilot studies, using early formulations. After single dosing, the apparent terminal TPV half-life was extremely variable, ranging from 2.3 to 44 hours. Tmax ranged from 1 to 5 hours between dose groups.
Steady state plasma levels were achieved within 6-10 days of initiating multiple dosing with a half-life of 2-4 hours. Early pilot studies with TPV alone showed increased clearance after multiple-dose resulting in a 2-3 fold decrease in AUC, which can be attributed to enzyme induction by TPV. Relevant steady state mean trough TPV concentrations > 1µM were observed for dose regimen of 900 mg t.i.d and higher.

Booster effect: In order to achieve effective TPV plasma concentrations and a b.i.d dosing regimen, co-administration of TPV with low dose RTV b.i.d is essential. RTV acts by inhibiting hepatic CYP3A, the intestinal P-glycoprotein efflux pump and possibly intestinal CYP3A as well. Hepatic CYP3A activity (as measured by the erythromycin breath test) increased from basal levels following administration of 500 mg TPV alone for 11 days, thus indicating CYP3A enzyme induction. When low-dose RTV is co-administered, the potent enzyme inhibition predominates and the net effect on CYP 3A is inhibition (% erythromycin metabolised per hour dropped to negligible). RTV was shown to act as a pharmacokinetic enhancer of TPV. However, as a result of enzyme turnover, CYP3A activity returned to baseline levels by day 3. These data confirmed that TPV and RTV must be taken together as recommended in the SPC.

TPV co-administered with RTV: After single dosing, peak plasma concentrations were reached within 1 to 5 hours after dose administration depending upon the dosage used.
With repeated dosing, TPV plasma concentrations were lower than predicted from single-dose data. Tipranavir induced its own metabolism prior to steady state even in the presence of ritonavir. Steady state was attained in most subjects after 7 days of dosing. The median Tmax ranged from 2-3 hours. The mean TPV half-lives ranged from 4-5 hours when TPV was given with 200 mg RTV.

TPV exhibited dose-proportional pharmacokinetics at steady state between 250 and 750 mg, when boosted by 200 mg RTV. TPV with low dose RTV (500/200 mg b.i.d) for 21 days was associated with a 29-fold increase in the geometric mean morning steady state trough plasma concentrations of TPV (compared to TPV 500 mg alone for 11 days). Co-administration of TPV at doses of TPV+ r 500/200 mg and above (given twice daily) consistently resulted in plasma TPV Cmin above 20 µM, more than 10 times the protein-adjusted IC_{90} for PI-resistant viral isolates grown in vitro. This target trough concentration of 20 µM was arbitrarily preliminary set for the dose selection as further discussed under the section "relationship between plasma concentration and antiviral activity".

Effect of food on soft capsules formulation

The influence of food was assessed in an open label study in healthy volunteers receiving a high fat meal after 4 days of bid dosing, and with a light snack after 7 days of bid dosing, with co-administered clarithromycin and TPV with RTV as part of an interaction study. Food significantly increased AUC0-12h by 31% (point estimate of 1.31, confidence interval 1.23 - 1.39) and C_{min} by 75% (point estimate of 1.75, confidence interval 1.55 - 1.97; n=21 evaluable subjects). It had less effect on C_{max} (increase by 16% point estimate 1.16, confidence interval 1.09 – 1.24). The design of the study was nonetheless open to criticism. Tipranavir is markedly induced even in the presence of ritonavir, and the steady state is not reached by Day 5. Hence, it was felt that the comparison of drug exposure between Day 5 and Day 8 would not capture the impact of food on tipranavir exposure, but rather the effect of induction. Nonetheless these limited data which suggest food may improve the pharmacokinetics of tipranavir, were viewed together with the existing recommendations to take ritonavir with food and the fact that tipranavir was more likely given with food in the pivotal studies. On this basis, the CHMP agreed to recommend the administration of TPV with low dose of RTV with food while waiting for the complementary study to be performed by the applicant, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Bioequivalence between oral solution and soft capsules formulation

An oral solution was developed intended for use in children and in patients who cannot swallow capsules. An open-label, randomised, three way crossover study has been conducted in 30 healthy volunteers to determine the relative bioavailability of TPV 500 mg oral solution with RTV 200mg compared to TPV 500 mg capsules with RTV 200 mg and to investigate the relative bioavailability of TPV 500 mg oral solution with RTV 200mg with food versus without food.

. In the fasted state, no bioequivalence between capsule and solution could be concluded. The solution was relevantly supra-bioavailable (37% for AUC and 50% fore Cmax).

. The oral solution given in fed state was supra-bioavailable (by 30% for AUC and 7% for Cmax) than the capsule given in fasted state.

The CHMP considered that waiting for further data to substantiate the interchangeability of capsule and oral solution to enable proper dosing recommendations, the oral solution was not approvable.

- Distribution

As no intravenous formulation for human use is available, the total volume of distribution is unknown. Inside the whole blood compartment, plasma protein binding of TPV is high (>99.9%) primarily to human serum albumin.

- Elimination

TPV alone is a potent CYP3A4 inducer with significant metabolism in this enzyme system.

When co-administered with RTV, TPV metabolites were not relevantly formed due to the inhibitory effect of RTV on CYP3A.

In plasma, unchanged TPV was predominant and accounted for at least 98.4% of the total plasma radioactivity circulating after dosing. Only a few metabolites were found in plasma, each of them was at trace levels (0.2% or less of the plasma radioactivity).

The total radioactivity recovery was 87.1% (range 21.3 to 91.2%) of administered dose (up to 264 hours). Most radioactivity was excreted between 24 and 96 hours after dosing.
Most TPV was excreted in the faeces (median stool recovery was 82.3%).
The median urine recovery was 4.4% (3.6-5.6%) of dose. Nearly the entire administered dose was excreted unchanged. Less than 5% of the administered ^{14}C-labeled TPV dose was excreted in faeces and urine as metabolites.

- Dose proportionality and time dependency

No formal study was conducted to investigate the dose proportionality of TPV given with 200 mg RTV. However, the available data showed a nearly proportional performance, at least regarding TPV trough plasma concentrations.

With respect to time-dependency, a diurnal variation in plasma tipranavir concentrations at steady state following TPV 500 mg given with 200 mg RTV BID was observed with morning trough values being as much as 22% higher than evening trough values. This diurnal pharmacokinetic variation is not expected to be clinically relevant.

- Special populations

Renal impairment

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

Hepatic impairment

An open-label, non-randomised study has been performed to investigate the influence of liver impairment on TPV given with 200 mg RTV bid pharmacokinetic parameters in patients with mild to moderate hepatic impairment (9 patients Child Pugh classification A and 3 patients Child Pugh classification B, no patients classified as Child Pugh C).

After multiple dosing in patients with mild hepatic impairment, the exposure (AUC) was 30% and the C_{min} 84% higher than in matched controls (C_{max} increased by 14%). After single dosing in patients with moderate hepatic impairment, TPV AUC and Cmax values were similar to those in healthy volunteers. In view of the limited data (not obtained at steady state), the applicant undertook to conduct a study assessing multiple doses of TPV with RTV in subjects with moderate hepatic impairment, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation. Waiting for these results, the CHMP agreed to recommend caution when administering TPV with low dose of RTV in patients with mild hepatic impairment, with increased monitoring frequency of hepatic tests as reflected in the SPC.
In the absence of data, tipranavir is contraindicated in patients with severe liver disease. The same recommendation applies for patients with moderate hepatic impairment for which the data are currently very limited.

Paediatric population

A phase I/IIa study has been conducted in treatment naïve and experienced children using the oral solution. Patients were stratified according to age (i.e 2 to < 6 years, 6 to < 12 years and 12 to 18 years) and randomised into one of the 2 different dose regimen: high dose group (TPV 375 mg/m^2 with RTV 150 mg/m^2) and low dose group (TPV 290 mg/m^2 with RTV 115mg/m^2). Only limited data from 37 children were available at the time of the opinion. Out of these 37 children, 33 received TPV with RTV for 4 weeks. The mean trough concentration was approximately 30% higher with the higher dose as compared to the lower dose. Considering the lack of bioavailability between the oral solution and the capsules and the very limited clinical data available, the CHMP agreed that tipranavir should

not be used in children. The provision of the final reports from this study is part of the follow-up measures to be fulfilled post-authorisation.

Influence of Gender, Race, Body weight, Age, HIV status

No specific PK study was performed investigating the influence of gender, race, weight and age on TPV with RTV PK.

The steady-state PK of TPV was assessed in 187 individuals (67 HIV-negative and 120 HIV-positive subjects) using 1866 TPV concentrations derived from 4 healthy volunteer studies and 2 patient studies. The final nonlinear mixed effects modelling (NONMEM) database consisted of 64.2% HIV+ patients, 35.8% HIV- subjects; 79.1% male, 20.9% female; 85% White Caucasians, 11% Black, 4% other; ranging from 18-73 years and 47-123 kg weight. TPV concentration-time data were fit to a 1-compartment model with first order absorption described in terms of absorption rate (Ka), apparent oral clearance (CL), and volume of distribution (V) parameters.

Population analysis showed that TPV apparent oral clearance could be significantly affected by HIV-status ($p<0.005$).
As shown in table 1, the pharmacokinetics exposure was higher in healthy volunteers than in HIV positive patients.

Table 1: NONMEM model-derived pharmacokinetic parameters for female and male HIV+ patients and HIV- subjects

Pharmacokinetic parameter*	HIV+ patients		HIV- subjects	
	Females (n = 14)	Males (n = 106)	Females (n = 25)	Males (n = 42)
$Cp_{0h,12h}$ (μM)	30.94	31.63	43.26	32.97
Cmax (μM)	92.33	75.87	114.71	90.08
Tmax (h)	2.9	2.9	3.0	2.9
AUC_{0-12h} (h•μM)	792.8	681.0	1005.3	781.8

The analysis showed also that TPV apparent oral clearance could be significantly affected by body weight ($p< 0.001$). Body weight caused the more prominent linear increase (75.7%) in apparent oral clearance. There was no effect of body weight on the volume of distribution of tipranavir. There were no or little effects of age or race on the clearance of tipranavir.
This analysis showed also that gender was a significant covariate as it relates to volume of distribution. Evaluation of trough TPV concentrations (10-14 h post-dose sample window) from the RESIST trials panelled by gender showed that females generally had higher tipranavir concentrations than males. After 4 weeks of TPV + RTV 500 mg/200 mg bid the median plasma though concentration of tipranavir was 43.9 μM for females versus 31.1 μM for males. The PK difference between females and males seem mainly driven by the weight. The safety and efficacy of TPV with low dose RTV will be further evaluated.

With respect to individual variability, it was relatively low for CL (CV = 32 %) and V (14 %) but higher for Ka (53 %).

No specific dosage adjustment is recommended based on the population PK results.

- Pharmacokinetic interaction studies

TPV is a substrate, an inducer and an inhibitor of CYP3A. When administered with low dose of RTV, there is a net inhibition of P450 CYP3A.

Several studies have been conducted to investigate the interaction profile of TPV with RTV with other commonly administered agents, mainly those metabolised via CYP 3A. The majority of these studies were performed in healthy volunteers.

Concerns were raised in relation to the design of the studies. The steady of tipranavir with ritonavir or of the combined medicinal product was not achieved in several studies. In addition a dose of tipranavir with ritonavir different from the recommended one (TPV + RTV 500/200 mg b.i.d) was used in several studies due to a late dose selection (e.g TPV with RTV 500/100 mg and TPV with RTV 750/200 mg b.i.d). In one study (with NRTI and NNRTI compounds) a high dose of TPV with RTV 1250/100 mg was also used. The CHMP agreed however that the data could be extrapolated for those interaction studies having used doses of TPV with RTV that bracket the recommended dose and that represent extremes capacities of hepatic enzyme induction and inhibition. The relevant information resulting from these studies has been reflected in the SPC.

Interaction with antiretroviral medicinal products

An open-label, multicentre, multiple dose study was conducted in HIV-1 patients to determine the PK effects of 3 doses of TPV with RTV (1250 /100 mg (n=58), 750/100 mg (n=63), 250/200 mg (n=87), all b.i.d) on the steady state PK of 7 nucleoside and non-nucleoside reverse transcriptase inhibitors. The results of this study showed:

Zidovudine and abacavir

There was a significant decrease in zidovudine and abacavir AUC (around 35 % and 40% respectively). The decrease was independent of the tipranavir dose. The mechanism of these interactions is unknown as well as the clinical relevance but further investigation will be conducted. The concomitant use of zidovudine or abacavir and TPV with RTV is therefore not recommended.

Didanosine (enteric coated capsule)

Significant decrease of didanosine exposure (AUC decreased up to 38%) was observed. The clinical relevance of this interaction is unknown. Since this interaction might be mainly driven by the food effect on didanosine absorption, resulting in a decrease in didanosine exposure, it is recommended to separate didanosine dose by at least two hours from the dose of TPV with RTV to avoid any formulation incompatibilities.

Lamivudine and stavudine

The co-administration did not cause a significant change in the AUC of lamivudine or stavudine and therefore no dosage adjustment is warranted**.**

Nevirapine and efavirenz

TPV with RTV decreased the AUC and C_{min} of nevirapine by approximately 10%. Nevirapine decreased tipranavir AUC by 15% and decreases the C_{min} by less than 5%.

TPV with RTV had no significant impact on the AUC and C_{min} of efavirenz meanwhile efavirenz, when co-administered with TPV with RTV 750 mg/200 mg reduced tipranavir C_{min} by 36 % after a single dose. After five days of dosing the tipranavir C_{min} returned to normal. With 500 mg/100 mg the initial reduction was 77 % and did not return to normal after five days. A concern was raised since the steady state plasma PK of TPV with RTV was not measured in the absence of the interacting compound thus preventing a direct comparison to quantify the effect of steady state of interacting compound on the TPV with RTV steady state PK. No definitive recommendations can therefore be drawn. Caution should therefore be exercised when co-administered and the applicant undertook to conduct further studies to assess the potential interaction with efavirenz, the results of which will be submitted as part of the follow-up measures to be provided post-authorisation.

Tenofovir

In a study in healthy volunteers, where patients received either TPV with RTV 500/100 mg or 750/200 mg with a single 300 mg doses tenofovir, TPV with RTV decreased the tenofovir Cmax in a dose dependent manner (decreased by 38% with high dose and 23% with lower dose) but had no effect on the extent of tenofovir AUC. Although this study was not conducted at steady state no major differences in the results are expected for these substances not metabolised by the CYP3A4. No dosage adjustment of tenofovir is therefore warranted.

Protease inhibitors

An open-label, randomised, 4 parallel-group, multiple dose, multicentre study was conducted to determine the change in C_{min} (at 12h) from week 2 (average of day 7 and 14) to week 4 (average of day 21 and 28) for the RTV-boosted saquinavir, amprenavir, lopinavir regimens following the addition of TPV with RTV 500/100 mg b.i.d. on day 14 in highly treatment experienced HIV-1 infected patients.

The trough levels, the Cmax and AUC were substantially reduced in the second PI groups after addition of TPV with RTV:

- For the patients on lopinavir/ritonavir there was a 55% decrease in AUC and 47% in Cmax.
- For the patients on amprenavir boosted there was a 44% decrease in AUC and 39% in Cmax.
- For the patients on saquinavir boosted there was a 76% decrease in AUC and 70% in Cmax.

The addition of TPV with RTV led also to a reduction of systemic RTV concentrations in the dual boosted periods. Therefore the concomitant administration of TPV with RTV with lopinavir/ritonavir, amprenavir or saquinavir boosted regimen, is not recommended, due to the major risk of lost efficacy of these protease inhibitors. If the combination is unavoidable, the SPC encourages monitoring protease inhibitors plasmatic level.

No interaction data are currently available with other boosted PIs.

Given the potential interest of dual boosted PIs in salvage therapy, the applicant undertook to further explore dose adjustment with boosted PIs.

Interaction with other substances:

Antacids

When TPV with RTV (500/200 mg bid) was co-administered with an antacid, the TPV AUC, Cmax and C12h were reduced by 25-29%. Therefore, the co-administration of TPV with RTV and the antacid should be separated for at least 2 hours.

Atorvastatin

In healthy volunteers, TPV with RTV (500/200 mg bid) at steady state increased the AUC of a single dose of 40 mg atorvastatin by approximately 9-fold and reduced the AUC of metabolites ortho-OH- and para-OH-atorvastatin by 89% and 82%, respectively. There are no data on the effects after multiple dosing of atorvastatin (i.e. when both treatments being in steady state), therefore the combination is not recommended. In addition the applicant undertook to perform an interaction study with pravastatin, the results of which will be submitted post-authorisation.

Clarithromycin

The effects of steady state TPV with RTV 500/200 mg b.i.d. on the steady state PK of clarithromycin 500 mg b.i.d. (and its major metabolite 14-hydroxy-clarithromycin) were evaluated in healthy volunteers. TPV with RTV increased markedly the C_{min} of clarithromycin by 68% and to a lesser extent the AUC (by 19%). There was no substantial change in C_{max}.

The formation of the active metabolite 14-OH-clarithromycin was nearly inhibited during co-administration of steady state TPV with RTV. The concentrations and exposure of 14-OH clarithromycin were reduced by more than 95%. The decrease in 14-OH-clarithromycin is of unknown clinical significance because the majority of pathogens susceptible to this compound are susceptible to clarithromycin itself, except in case of *Haemophilus influenzae*, where the 14-OH metabolite is twice as active as the parent compound. A warning has therefore been included in the SPC.

Ethinyl estradiol and norethindrone

In healthy volunteers, the addition of TPV with RTV b.i.d. (500/100 mg or 750/200 mg) to EE/NET reduced the total EE AUC by 43-48% and the EE Cmax by approximately 50%. There was an increase of 13-27% NET AUC but this was considered of minor clinical relevance. The co-administration of oestrogen based oral contraceptives with TPV with RTV is therefore not warranted because of reduced efficacy of the contraceptives.

Fluconazole

The effects of single-dose and steady state TPV with RTV 500/200 mg b.i.d. on the steady state PK of fluconazole 100 mg qd (200 mg loading dose) were evaluated in healthy volunteers.
The PK of fluconazole was not relevantly altered by TPV with RTV. Fluconazole increases the AUC and C_{min} of TPV by 56% and 104%, respectively, when compared to historical data. No dosage adjustments are recommended.

Loperamide

Steady state TPV with RTV 750/200 mg b.i.d, reduced loperamide AUC by 51% and Cmax by 61% and N-demethyl-loperamide AUC by 77% and Cmax by 79%. There was also a reduction of TPV Cmin (26%) by loperamide. The clinical relevance of these changes is unknown.

Rifabutin

TPV with RTV (500/200 mg b.i.d) at steady state caused a substantial and clinically relevant increase in AUC of rifabutin of 3-fold and of 21-fold of the rifabutin desacetyl metabolite. The Cmax of rifabutin increased 4.3-fold. Although this study only investigated the effect of a single dose of rifabutin, a reduction of rifabutin dosing regimen is warranted as well as a monitoring of patients for emergence of adverse reactions associated with rifabutin.

The interaction profile of TPV with RTV is complex. The applicant undertook to complete the interaction programme, including interaction studies with methadone, buprenorphine, omeprazole as well as in-vitro investigations of the potential induction of TPV with RTV and the role of the organic anion transporter peptide (OATP2).

Pharmacodynamics

- Mechanism of action

As already mentioned in section 3.3 of this document, tipranavir is a non-peptidic protease inhibitor which has been shown to be active against HIV-1.

- Primary and secondary pharmacology

Resistance in vitro

In vitro resistance studies conducted with wild type virus over a period of 9 month (70 passages) in culture showed that resistance to TPV developed in very small incremental steps. The first mutations selected during these experiments were mutations L33F and I84V, at passage 16, followed by K45I, I13V, V32I, V82L, M36I, A71V, L10F and I54T/V. The mutations L33F and I84V (among the exclusion criteria in clinical studies) gave very little level of resistance to TPV. The mutation V82L alone did not confer increased resistance to TPV greater than 1.6-fold. With increasing number of mutations an increase in resistance to TPV developed, showing a 16-fold resistance in the presence of 6 mutations raising to about 69-fold with 10 mutations. These TPV-resistant viruses, however, had a decreased ability to replicate in vitro.
The susceptibility of 2 clones containing 6 and 10 mutations respectively, was decreased (≥10-fold) to all protease inhibitors tested except for saquinavir for which no more than 2.5 fold resistance was observed.

TPV maintained activity (<4 fold resistance) against the majority of HIV isolates showing decreased susceptibility to amprenavir (81% remain susceptible to TPV), atazanavir (2/2 isolates remain susceptible to TPV), indinavir (88% remain susceptible to TPV, nevirapine (88% susceptible to TPV), lopinavir (83% susceptible to TPV), RTV (89% susceptible to TPV) and saquinavir (88% susceptible to TPV). 2.3% of all isolates showed > 10-fold resistance to TPV.
The TPV IC90 for multidrug resistant clinical HIV isolates ranged from 0.31-0.86µM, and most clinical HIV isolates had a serum-adjusted IC90 of ≤2µM.

Resistance in vivo

The applicant provided a comprehensive review of resistance data obtained from Phase II and III clinical trials.

Long-term resistance data are available for 276 patients treated with TPV with RTV in the Phase II and III clinical trials. Paired baseline and on-treatment genotypic and phenotypic resistance testing results were evaluated for HIV-1 isolates from 145 patients in Phase II Trials 1182.2, 1182.4 and 1182.52 (including the rollover BI 1182.17), 72 patients in BI 1182.51 and 59 patients in RESIST trials. The median time on treatment of samples included in these analyses was as follows: 54 weeks for Phase II trials (range 7-202 weeks), 19 weeks for BI 1182.51 in more PI experienced patients (range 6-25 weeks) and 48 weeks for Phase III RESIST trials (range 8-64 weeks).

Overall, the analyses of Phase II demonstrated that the predominant emerging mutations with tipranavir used in HAART regimens are L33F/I, V82T/L and I84V.
The data from the RESIST trials were in line with the virological analysis from Phase II studies since the most common protease mutations emerging after TPV exposure in patients with PI-experienced patients were consistently L33F/I/V, I84V and V82L/T. These mutations, and in particular mutations at codons 33 and 84, impact on tipranavir susceptibility, the mutation at codon 90 alone having a limited impact on phenotypic susceptibility to TPV/r.

Data on resistance from RESIST trials, the design of which is presented later in this document, have also been submitted.

The susceptibility of virus in the 59 patients with virologic failure was evaluated for other available protease inhibitors for both baseline and on-treatment samples. The median IC_{50} showed resistance for all PIs except TPV at baseline. Although the median IC_{50} for lopinavir, amprenavir and indinavir decreased between baseline and last determination on treatment (LPV 101.8 to 63.2; APV 21.5 to 14.8 and IDV 52.2 to 46.8) these PIs remained resistant. There were small increases in IC_{50} between baseline and last determination for atazanavir (73.6 to 76.6) and for nelfinavir (44.6 to 48.9). Saquinavir was the only protease inhibitor with a large increase in IC_{50} between baseline and last determination (37.7 to 50.2).

Fifty-two patients in the RESIST trials had paired baseline and on-treatment phenotypic susceptibility results (Table 2). The median baseline TPV phenotype for all patients in this analysis was 1.8-fold IC_{50}, and the median on-treatment phenotype was 12.8. The baseline TPV IC_{50} of these patients was higher than the whole RESIST population tested. If expressed as proportion of isolates resistant to TPV, defined as > 4-fold IC_{50}, only 20% of patients were resistant at baseline where as 85% of patients were resistant on treatment.

Table 2 Comparison of baseline to on-treatment phenotype: Virologic Failure Patients of RESIST Trials

	Last on-treatment phenotype (FC in IC_{50})		
Baseline phenotype (FC in IC_{50})	<1 n/N (%)	1 to <4 n/N (%)	>=4 n/N (%)
<1	0	0	8/8 (100.0)
1 to <4	4/34 (11.8)	1/34 (2.9)	29/34 (85.3)
>=4	0	3/10 (30.0)	7/10 (70.0)

From the combined RESIST studies, the baseline genotypic testing demonstrated that the most common key codon mutation pattern observed in patients in the two arms were:

- 82 and 90, n=252;
- 84 and 90, n=209;
- 84 only, n=184;
- 33 and 82, n=170;
- 90 only, n=97.

The baseline combination of 82 and 84 was observed in 62 patients.

Looking at the primary endpoint treatment response (confirmed 1 log drop in viral load from baseline) for a variety of patterns in baseline key codon mutations, the data demonstrated that a higher proportion of patients had a 1 log drop treatment response if they received tipranavir for nearly all of the possible patterns of baseline mutations at positions 33, 82, 84 or 90, as compared with the CPI/r arm. Overall, there were 53.2% of patients included in the RESIST trials who had at least one key mutation at codon 90. Whereas the mutation at codon 90 (which was part of the inclusion criteria) has been later shown not to have any significant influence on TPV susceptibility, the same does not apply for other PIs (especially mutation L90M that impact most of PIs). This is also true for the mutation 82 (especially V82A; the mutation V82L that impact TPV susceptibility was only present in less than 2% of patients at baseline).

Overall the resistance data are difficult to interpret. Resistance data from further ongoing clinical studies will be submitted as part of the follow-up measures to be fulfilled post-authorisation to further substantiate the resistance profile for TPV.

Relationship between plasma concentration and antiviral activity

The target trough concentration of 20µM was preliminary set on in vitro results for the dose selecting process.

In the dose ranging studies, relationship of change in viral load from baseline to day 14 and tipranavir trough plasma concentration showed that in the TPV with RTV 500/200 group, 15.8% of patients (n=10) with Ctrough < 20µM and 36.5% of patients (n=23) with Ctrough > 20µM had a limited viral load reduction between 0 and –1 log at day 14.
In the main RESIST studies, described later in the document there seemed to be a relationship between TPV trough concentrations and virologic response. In patients with Ctrough levels of 19.5 to 26.5 µMol, the median change in viral load at week 24 was log - 0.38 copies/ml compared to log – 1.69 to –2.09 in patients with Ctrough levels > 39 µMol.

Relationship between inhibitory quotient (IQ) and virologic response:

The virologic response to TPV/r therapy has been evaluated with respect to baseline IQ in highly treatment-experienced patients. The IQ was determined by dividing the TPV trough concentrations by the protein-adjusted IC50 of the baseline virus. In the phase II trial, an IQ of approximately >30 to 100 appeared a limit to achieve a significant viral load decrease > -1 log_{10} in each treatment arms after 2 weeks of functional monotherapy. In the Resist trials a number of patients had a TPV IQ < 30 (n=87, 26.4% of patients) and < 60 (n=145, 44% of patients). Modest median VL reduction at Week 24 for patients with a TPV IQ of below 60 was observed (between –0.04 and –0.62 log_{10} copies/ml). Patients with TPV IQ > 60 obtained greater median viral load reduction between –1.24 and –2.12 log_{10} copies/ml.

Due to the high variability in TPV Ctrough, the applicant undertook to further explore PK/PD relationship to eventually define thresholds of TPV concentrations above or below which excess toxicity or inadequate virologic response is seen.

Clinical efficacy

Dose ranging studies

An overview of the studies is provided in table 3.

Table 3: overview of dose ranging studies

Protocol Number	Title of the study and Study Design	Population and Number	Treatment Dose (mg)
1182.2	Open-label Randomised exploratory study of TPV and RTV in combination with one NRTI and efavirenz in multiple protease inhibitor-experienced HIV patients Planned to 24 weeks but further extended to 48 and 96 weeks	HIV-1 infected patients CD4 ≥ 50 cells/mm^3 VL ≥ 5000 copies/ml PI experienced (who have failed ≥ 2 PI regimens) NNRTI naïve 41 enrolled 19 in the low dose TPV 22 in the high dose TPV 29 completed 48 weeks	TPV Hard filled capsules (HFC) 300mg initially and changed to TPV SEDDS formulation 250mg TPV doses HFC dose: 1200mg or 2400mg BID SEDDS dose: 500mg or 1000mg BID RTV doses: 100mg or 200 mg BID with TPV HFC 100mg BID taken with TPV SEDDS
1182.3	Open-label, randomised, parallel group study	HIV-1 infected patients treatment naïve 31 randomised	3 treatment arms: TPV 1200 mg TPV/RTV 300/200mg TPV/RTV 1200/200mg
1182.4	An open-label, randomised study comparing combination therapy (TPV and RTV versus SQV and RTV) used with two NRTIs in single PI-experienced HIV-1 patients Planned to 24 weeks but further extended to 48 and 96 weeks	HIV-1 infected patients VL ≥ 1000 copies/ml No limit of CD4 With clinical failure while on the current PI-containing regimen of IDV, NFV or APV received since at least 6 months 81 randomised (1:1:1) 79 treated	3 treatment arms: TPV/RTV 500/100mg BID + 2NRTIs TPV/RTV 1250/100mg BID + 2 NRTIs SQV/RTV 400/400mg BID + 2 NRTIS TPV SEDDS formulation soft elastic capsules 250mg
1182.52	Double-blind randomised, dose optimization trial of 3 doses of TPV boosted with low dose RTV in multiple antiretroviral experienced subjects. On study entry, patients discontinued their original PI(s) and began oral administration of 1 of the 3 blinded regimens while continuing to take their other background ARV medications After 2 weeks of therapy with their original ARV background therapy and TPV/r, patients had their background ARV optimised based on the genotypic resistance testing performed at screening and on their history of ARV use	Treatment-experienced HIV-1 infected patients with screening genotypic resistance indicating: - at least 1 primary PI mutation at sites 30N, 46I, 46L, 48V, 50V, 82A, 82L, 82T, 84Vor 90M, and - no more than 1 PI mutations of 82L, 82T, 84V or 90M > 3 months of experience with NRTIs, NNRTIs and PIs with current PI-based ARV medication for at least 3 months prior to randomization, > 3 months of experience with at least on other PI-based regimen HIV-1 viral load ≥ 1 000 copies/ml, any CD4+ cell count	Group A: TPV 500mg BID + RTV 100mg BID Group B: TPV 500mg BID + RTV 200mg BID Group C: TPV 750mg BID + RTV 200mg BID Planned: 165 Entered/randomized: 216 (Group A: 73, Group B: 72, Group C: 71) Analysed: 200 (Group A: 69, Group B: 67, Group C: 64)

The first three studies were considered of limited interest due to issues related to their design (e.g no use of the final SEDDS formulation of tipranavir, ritonavir dose different from the final recommended one and no use of the claimed dose of TPV with RTV of 500/200mg BID). They confirmed that TVP had an "intrinsic" antiretroviral activity, and that TPV should be boosted by RTV.

In study 1182.52 although the primary endpoint (viral load reduction of ≥ 0.5log 10 copies/ml after two weeks of TPV with RTV therapy) was not statistically significant between the three treatment arms, a trend towards a dose-effect could be observed (table 4).

Table 4: Median log_{10} change from baseline in Viral load after 2 weeks of TPV/r Treatment (Full analysis set)

Type of Analysis	Treatment Group						
	TPV/r 500/100		TPV/r 500/200		TPV/r 750/200		All TPV/r
	N	Median	N	Median	N	Median	χ^2 (p-value)[a]
LOCF	73	-0.85[b]	72	-0.93[b]	71	-1.18[b]	2.913 (0.2330)
OT	70	-0.87[b]	68	-0.96[b]	66	-1.19[b]	2.863 (0.2389)

a Chi-square statistic and significance value from the Kruskal-Wallis test with 2 df.
b $p<0.0001$ based on the Wilcoxon signed rank test.
LOCF: last observation carried forward; OT: on treatment

In terms of viral load change from baseline over time, efficacy results were better with higher doses. At week 24, the proportion of patients with > 1 log_{10} reduction from baseline and the proportion of patients with viral load < 400 copies/ml were higher in the TPV with RTV 500 mg/200mg and 750mg/200 mg than 500/100 mg: 40.3 % versus 45.1 % versus 31.5 % respectively and 37.5 % versus 38 % versus 32.9 % respectively. More patients discontinued prematurally the TPV + r 750/200 mg arm (31 %) and 500 mg/100 mg (21.9 %) compared to 500 mg/200 mg (16.7 %). The most common reason for discontinuation in each arm was adverse events (6.8 % versus 9.7 % versus 15.5 % in 500 mg/100, 500 mg/200 and 750 mg/200 mg respectively). In terms of safety, there was a trend towards of a dose relationship of hepatic enzyme elevations: Grade 3-4 ALT and GGT 4/73 (5.5%) and 12 (16.4%) in TPV/r 500/100 versus 8/72 (11.1%) and 23 (31.9%) in TPV/r 500/200 versus 15/71 (21.1%) and 25 (35.2%) in TPV/r 750/200.
Considering on one hand the efficacy results that show close virologic responses between the intermediate (500/200) and the highest dose (750/200) and on the other hand the hepatic events as a concerning limiting factor for increasing the dose, the intermediate 500/200 mg dose was selected for the main clinical studies.

Clinical efficacy

Two main ongoing, open label, randomised, comparative safety and efficacy studies of TPV boosted with low dose RTV in relation to genotypically-defined protease inhibitor/ritonavir (PI/RTV) in multiple antiretroviral experienced patients have been conducted:

- RESIST 1 (USA, Canada, Australia involving about 600 patients)
- RESIST 2 (European and Latin America involving about 800 patients)

METHODS

Study Participants

For both studies, the inclusion criteria consist of highly treatment-experienced HIV-1 infected males or females patients ≥18 years of age with screening genotypic resistance report indicating both of the following:

- at least one primary PI mutation at sites 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M, and
- no more than two protease mutations on codons 33, 82, 84 or 90

Patients had to have at least 3 consecutive months experience taking ARVs from each of the classes of NRTI(s), NNRTI(s) and PI(s) with:

- at least 2-PI based regimens, one of which must be the current regimen, and
- current PI-based ARV medication for at least 3 months prior to randomisation

Patients are failing their current PI regimen (HIV-1 viral load > 1 000 copies/ml at screening, any CD4+ cell count). An amendment was made to the protocol to allow with highly protease inhibitor resistant virus to be treated with a ritonavir boosted PI-based regimen.

Treatments

Eligible patients had to be randomly assigned to one of the following open-label treatments:

- TPV 500mg b.i.d + RTV 200mg b.i.d + concomitant optimised background ARV medications (OBR). TPV with RTV may be taken with or without food. Intake with food was recommended to reduce the potential for nausea and vomiting.

Boosted comparator protease inhibitor (CPI/r) arm: pre-selected PI + low-dose RTV (100 or 200mg, according to product label or published recommendations) + concomitant OBR. The boosted PI could be chosen between amprenavir (APV/r 600/100 mg bid), indinavir (IDV/r 800/100 mg bid), lopinavir (LPV/r 400/100 mg bid) or saquinavir (SQV/r 1000/100 mg bid or 800/200 mg bid).
Before randomisation, the comparator protease inhibitor (CPI) was to be selected by the physician based on genotyping results. A panel of HIV-resistance consultants was put in place to review comparator PI selections made by the investigator (selected cases included those in which an investigator wished to recommend a PI that did not represent the best option according to the genotype report). Whereas a systematic consultation of the experts panel could have conferred robustness in the efficacy demonstration, this consultation occurred only for planned selected cases.

The randomisation was stratified both by pre-selected boosted PI (lopinavir, indinavir, saquinavir or amprenavir) and by use of enfuvirtide.

Patients in the comparator arm who had a lack of initial virologic response or a confirmed virologic failure at any time after the first 8 weeks of the both studies were offered the opportunity to enrol into long-term safety trial 1182.17. CPI/r patients who experienced intolerance or toxicity were not to be offered enrolment into trial 1182.17, but rather were to be provided a standard of care therapy.

Objectives

The objective of the RESIST studies (randomised evaluation of strategic intervention in multi-drug resistant patients with tipranavir) was to demonstrate the safety and efficacy of TPV with low dose RTV versus an active control arm in highly experienced HIV-1 infected patients.

Outcomes/endpoints

The primary endpoint was the proportion of patients at 48 weeks with treatment response and the time to treatment failure through 48 weeks.

Treatment response was defined as a confirmed virologic response, defined as two consecutive viral load (VL) measurements $\geq$ 1 $\log_{10}$ below baseline without prior:

- two consecutive VL measurement < 1 $\log_{10}$ below baseline after two consecutive VL measurements $\geq$ 1 $\log_{10}$ below baseline
- One VL of < 1 $\log_{10}$ below baseline followed by permanent discontinuation of the study drug or lost to follow-up after two consecutive VL measurements $\geq$ 1 $\log_{10}$ below baseline

Time to treatment failure was defined as Day 0 for patients who never achieved a confirmed virologic response before one of the following events:

- Death
- Permanent discontinuation of the study drug or lost to follow-up
- Introduction of a new ARV drug to the regimen (if it was not solely related to either toxicity or intolerance that was clearly attributable to a background drug, but not the study drug or its control), or
- Last available visit

Time to treatment failure for patients who achieved a confirmed virologic response was the earliest time of:

- Death
- Permanent Discontinuation of the study drug or lost to follow-up

- Introduction of a new ARV drug to the regimen (if it was not solely related to either toxicity or intolerance that was clearly attributable to a background drug, but not the study drug or its control),
- First occurrence of a confirmed virologic failure, or
- One VL measurement that represented a drop of < 1 $\log_{10}$ below baseline, followed by permanent discontinuation of the study drug or loss to follow-up.

Secondary endpoints included:

- for RESIST 1, the proportion of patients at 24 weeks with $\geq$ 1 $\log_{10}$ reduction in two consecutive viral load measurements without prior evidence of treatment failure.

- for RESIST 2, the proportion of patients with a virologic response at 16 weeks ($\geq$ 1.0 $\log_{10}$ reduction in viral load without prior evidence of treatment failure + Treatment response (TR) at Week 24.

Among other secondary endpoints (RESIST 1 and 2) there were the change from baseline in viral load, proportion of treatment and virologic responders at each study visit, change from baseline in CD4+ and CD8+ cell counts, genotypic and phenotypic resistance patterns, assessment of patient adherence, evaluation of the inhibitory quotient (IQ) = PI C_{min}/IC_{50}, evaluation of safety and quality of life.

Sample size and statistical methods

For RESIST 1, sample size estimations were performed for both primary efficacy endpoints to detect superiority. Since treatment response at 24 weeks requires a larger sample size than treatment failure at 48 weeks, treatment response at week 24 was used to determine the sample size. The study was sized to detect a 15% superiority of treatment with TPV/r in treatment response at 24 weeks with 90% power using a Fisher's exact test at the 5% level of significance (two-sided). This procedure resulted in a sample size of 247 patients per treatment group if the response rate was 35% in the control group and 50% in the TPV/r group.

For RESIST 2, sample size estimations were performed for both primary efficacy endpoints to detect superiority. Since virologic response at Week 16 requires a higher sample size than treatment failure at 48 weeks, virologic response at Week 16 was used to determine the sample size.
The study was sized to detect a 10% superiority of TPV with RTV in virologic response at 16 weeks with a power of 80% using a Fisher's exact test. This procedure resulted in a sample size of 404 patients per group if the virologic response rate is 40% in the control group and 50% in the TPV with RTV group.

The following patient populations were analysed:

- Full Analysis Set (FAS): all randomised patients who received at least one dose of study medication
- Per Protocol Set (PPS): all patients in the FAS without relevant protocol deviations
- All randomised patients (ARP): all randomised patients including those that did not take study medication

The key efficacy analyses were based on FAS. The PPS at week 24 (=PPS24) and ARP sets were used for the sensitivity analysis.

The following types of analyses were used to assess the impact of missing data on the efficacy endpoints of the study:

On treatment (OT): Missing values were not replaced or imputed.

Non-completers considered failure (NCF): This analysis, where missing values due to premature discontinuations of the study drug were replaced by failures, was only applicable for binary endpoints. Isolated missing values, which were preceded and followed by a response, were considered a response. If the last visit to be included in the analysis (Week 24 for interim analysis) was missing, the

patient had a response at the last available visit and the patient did not have an indication of premature drug or trial discontinuation, the response was carried forward to the last visit (Week 24 for the interim analysis). All other missing data were considered failures.
Last observation carried forward (LOCF): Missing values during the course of study treatment were replaced by the measurement for the preceding visit. If the first on-treatment visit measurement was missing, the calculated baseline value was used for the visit.
Non-completers considered censored (NCC). For time-to-event data, patients who discontinued before the event was observed were considered censored.

There were a number of amendments made to the protocols. Among them, there was the possibility to add enfuvirtide, however the stratification by enfuvirtide was mandatory given the potential deleterious impact in the interpretation of the results.

RESULTS

At the time of submission of the application, only the results on the secondary endpoints are available (i.e. proportion of patients with $\geq$ 1 $\log_{10}$ reduction in viral load from baseline without prior evidence of treatment failure at medium term of 24 weeks for RESIST 1 and 16 weeks for RESIST 2 (24 weeks data are only available for approximately 60% of the randomised population in the latter study). Updated efficacy data were submitted during the procedure, including 24 weeks for the whole population for the RESIST-2. These studies are ongoing and are expected to provide long term data up to 96 weeks**.**
Data from both RESIST trials are suitable for pooling since the designs of the two studies were essentially identical except for the timing of interim trial endpoints, larger sample size in RESIST 2, and genotypic resistance testing used (logistic issue related to geographical location of laboratories).

Participant disposition

Table 5: RESIST 1: Disposition of all patients – FAS (as randomised)

	Treatment group/No (%) of patients					
	TPV/r		**CPI/r**		**Total**	
Screened / enrolled	--		--		1406	
Randomised / entered	313		317		630	
Not treated	2		8		10	
Total treated	311	(100.0)	309	(100.0)	620	(100.0)
Disposition through Week 8[a]						
Not prematurely discontinued before or at week 8	286	(92.0)	275	(89.0)	561	(90.5)
Prematurely discontinued before or at Week 8[b]	25	(8.0)	33	(10.7)	58	(9.4)
Missing or incomplete data at Week 8	0		1	(0.3)	1	(0.2)
Disposition through Week 24[c]						
Not prematurely discontinued before or at Week 24	263	(84.6)	151	(48.9)	414	(66.8)
Prematurely discontinued before or at Week 24[d]	48	(15.4)	139	(45.0)	187	(30.2)
Missing or incomplete data at Week 24	0		19	(6.1)	19	(3.1)

a The Week 8 visit (Visit 6) was nominally at Day 56 but a time window of 43 to 84 days was used
b Prematurely discontinued from trial medication # 84 days after start of study treatment
c The week 24 visit ((Visit 8) was nominally at Day 168 but a time window of 141 to 196 days was used
d Prematurely discontinued from trial medication # 196 days after start of study treatment

The imbalance between the rate of premature treatment discontinuation before or at week 24 is mainly driven by the lack of initial virologic response (1 in TPV/r group versus 31 in CPI/r) and confirmed virologic failure (4 in TPV/r versus 71 in comparator group).
Treatment discontinuation in relation to adverse events was more frequent in TPV arm (3 versus 1).

As for RESIST 1, a significant number of patients (10.6%) in RESIST 2 had missing or incomplete data at Week 24 with a noticeable difference between the two treatment groups (17.9% in the CPI/r arm versus 3.3% in the TPV/r arm).

Table 6: RESIST 2 - Disposition of patients who reached or could have reached 24 weeks in trial, FAS24 (as randomised)

	Treatment group/No (%) of patients		
	TPV/r	**COI/r**	**Total**
Screened / enrolled			1903
Randomised / entered	274	273	547
Not treated	3	5	8
Total treated	271 (100.0)	268 (100.0)	539 (100.0)
Disposition through week 8[a]:			
• Prematurely discontinued before or at week 8	17 (6.3)	29 (10.8)	46 (8.5)
Disposition through week 16[b]:			
• Not prematurely discontinued before or at week 16	233 (86.0)	175 (65.3)	408 (75.7)
• Prematurely discontinued before or at week 16	38 (14.0)	93 (34.7)	131 (24.3)
• Missing or incomplete data at week 16	0 (0.0)	0 (0.0)	0 (0.0)
Disposition through week 24[c]:			
• Not prematurely discontinued before or at week 24	212 (78.2)	96 (35.8)	308 (57.1)
• Prematurely discontinued before or at week 24	50 (18.5)	124 (46.3)	174 (32.3)
• Missing or incomplete data at week 24	9 (3.3)	48 (17.9)	57 (10.6)
a : Termination of trial medication <= 84 days after start of treatment b : Termination of trial medication <= 140 days after start of treatment c : Termination of trial medication <= 196 days after start of treatment			

Again, there was an imbalance between the rate of premature treatment discontinuation between the two treatment arms, mainly due to a higher proportion of patients who had a lack of initial response or a confirmed virologic failure at week 16 in the comparator arm compared to the TPV/r arm (4.9% vs 0.9% and 15.4% vs 0.5% respectively).

Baseline data

Patients included in RESIST 1 study had a mean age of 45.1 years old, were mainly male (91.1%) and White Caucasians (76.8%). Only 55 females were included in the study (8.9%).

In RESIST 2 study, the mean age of patients was 42.7 years. Most patients were male (82.9% of male versus 17.1% of females) and White Caucasians (73.8%).

The baseline disease characteristics were well balanced between the two treatment groups. As highlighted in the table 7, these studies have enrolled heavily pre-treated patients at an advanced stage of the disease.

Table 7: HIV baseline characteristics – FAS (as randomised)

	RESIST-1	**RESIST-2**
Nb of patients (total treated)	**620**	**863**
Baseline HIV RNA [log_{10} copies/ml] Median	4.83	4.77
Mean	4.74	4.73
SD	0.70	0.67
Range	2.01-6.31	2.97-6.76
Baseline CD4+ count [cells/mm^3] Median	123	185.0
Mean	164	218.0
SD	162	180.0
Range	1-1184	2-1893
CDC class C	57.1%	55.8%*
CD4 < 200 mm^3	67.1%	52.4%
CD4 < 50 mm^3	30%	16%
VL > 100 000 copies/ml	40%	34.5%
Median number of prior Antiretroviral agent received (range)	12 (3-20)	12 (3-18)

* data on only on 539 randomised and treated patients (FASS24)

Overall, the proportion of patients with HBV or HCV co-infection was limited (around 10%). A higher proportion of CPI/r patients (7.4%) versus TPV/r patients (3.2%) had a hepatitis C co-infection.

The population enrolled was to match precise inclusion criteria as regards the genotypic resistance at baseline (at least one PRAM at sites 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M, and no more than two protease mutations on codons 33, 82, 84 or 90). In practice, a heterogeneous population of heavily pre-treated patients has been enrolled (with or without any "genotypically available" boosted PI remaining). The distribution of protease gene mutations was balanced between the two study arms.

Most patients included in both arms had the combination of the two key mutation at codons 82 and 90 (n=177 in TPV/r arm and n=158 in CPI/r arm i.e 22.5% of included patients) or the combination of mutations at codons 84 and 90 (n=112 in TPV/r arm and n=136 in CPI/r arm i.e 16.7% of patients). Overall, they were 53.2% of patients included in the RESIST trials who had at least one key mutation at codon 90. Whereas the mutation at codon 90 (which was part of the inclusion criteria) has been later shown not to have any significant influence on TPV susceptibility, the same does not apply for other PIs (especially mutation L90M that impact most of PIs). This is also true for the mutation 82 (especially V82A; the mutation V82L that impact TPV susceptibility was only present in less than 2% of patients at baseline).

With respect to the selected PI, in RESIST-1, a majority of patients were treated by LPV in the comparator arm (61%) followed by SQV (20.6 %) and APV (14 %). IDV was rarely pre-selected (4.4%). The same pattern was noted in RESIST-2, with the most frequent pre-selected PIs were LPV (38%) and APV (39.5%). IDV was rarely pre-selected (2.6%).

Conduct of the studies

- Use of enfuvirtide

In RESIST 1, 224 patients out of 620 **(**36.1%) received enfuvirtide as concomitant medication (most patients (53.1%) were in the TPV/r arm compared to 46.8% of patients in the CPI/r arm).
In RESIST-2, there was a lower proportion of patients than in RESIST 1 who received concomitant enfuvirtide. Only 62 patients (11.5%) were treated with enfuvirtide (14.3% in the TPV/r arm and 8.5% in the CPI/r arm).

- Relevant protocol deviations

A high number of protocol deviations (around 40 %) was identified. The list of common protocol deviations is shown in table 8.

Table 8: Patients with Relevant Protocol Deviations for Categories for RESIST & RESIST 2 Studies Combined

RESIST 1 & RESIST 2		
Protocol Deviation	**TPV/r**	**CPI/r**
No protease gene mutations at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M	11	4
More than two protease gene mutation at codons 33, 82, 84, 90	20	21
Less than 2 PIs or less than 3 months of treatment on historical HIV-1 therapy page	9	11
No NRTI with> 1 month duration or no NNRTI > 1 month duration	9	10
Screening viral load <1000	7	2
ALT or AST > DAIDS grade 1	18	23
Triglycerides at screening > DAIDS grade 2	43	60
No new or recycled ARV in OBR	**50**	**53**
Wrong Enfuvirtide stratum	**21**	**28**
OBR of less than 2 non PI ARV drugs	7	7

The concern raised with respect to the protocol deviation "wrong enfuvirtide strata" is further discussed under the outcome section.

- switch after 8 weeks

During the first 8 weeks patients were not allowed to roll over into trial 1182.17, and during the first 8 weeks roughly 90% of patients randomised in both trials and both arms have not had prematurely discontinued the trials.

Outcomes

Treatment efficacy outcomes for both studies are displayed in table 9.

Table 9: Treatment outcome at Week 24 – RESIST trials (FAS [NCF])

	RESIST 1		RESIST 2		Total	
	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)	TPV/r N (%)	CPI/r N (%)
Total treated	311 (100.0)	309 (100.0)	271 (100.0)	268 (100.0)	582 (100.0)	577 (100.0)
Treatment response at Week 24	129 (41.5)	69 (22.3)	111 (41.0)	40 (14.9)	240 (41.2)	109 (18.9)
No confirmed 1 log_{10} drop from baseline	140 (45.0)	209 (67.6)	127 (46.9)	203 (75.7)	267 (45.9)	412 (71.4)
1 log_{10} drop from baseline without confirmation	31 (10.0)	16 (5.2)	19 (7.0)	16 (6.0)	50 (8.6)	32 (5.5)
Rebound[a]	51 (16.4)	39 (12.6)	38 (14.0)	24 (9.0)	89 (15.3)	63 (10.9)
Never suppressed through Week 24	45 (14.5)	45 (14.6)	46 (17.0)	57 (21.3)	91 (15.6)	102 (17.7)
Drug change or discontinuation due to virologic failure[b]	13 (4.2)	109 (35.3)	24 (8.9)	106 (39.6)	37 (6.4)	215 (37.3)
Death[c]	5 (1.6)	3 (1.0)	1 (0.4)	2 (0.7)	6 (1.0)	5 (0.9)
Study drug discontinuation due to adverse events[d]	25 (8.0)	9 (2.9)	22 (8.1)	13 (4.9)	47 (8.1)	22 (3.8)
Study drug discontinuation due to other reasons	12 (3.9)	19 (6.1)	10 (3.7)	10 (3.7)	22 (3.8)	29 (5.0)

a Confirmed loss of virologic response or loss of virologic response and missing confirmatory visit.

b Includes premature discontinuation of the study PI due to virologic failure and the addition of a drug to the background regimen (if not introduced to replace a background drug discontinued due to AEs attributable to the discontinued background drug).

c Death as primary reason for treatment failure.

Table 10: Resist-1 Key and sensitivity analysis of treatment response at Week 24 for impact of open-label design and handling of missing data:

	Treatment group		Treatment difference[a]		
	TPV/r n/N (%)	CPI/r n/N (%)	Weighted Diff. (%)	95% CI LL(%)	UL (%)
Key analysis					
FAS (NCF, as randomised)	129/311 (41.5%)	69/309 (22.3%)	18.4%[b]	11.4%	25.3%
Sensitivity analysis					
PPS24 (NCF, as randomised)	86/191 (45.0%)	50/193 (25.9%)	18.5%[b]	9.3%	27.6%
FAS (TPV-NCF CPI-NCC, as randomised)	129/311 (41.5%)	69/291 (23.7%)	17.0%	9.9%	24.1%
FAS (NCC, as randomised)	129/305 (42.3%)	69/291 (23.7%)	17.7%	10.5%	24.8%
Confirmed virologic response – FAS (OT, as randomised)	128/265 (48.3%)	68/156 (43.6%)	3.7%	-5.8%	13.2%
Confirmed virologic response – FAS (NCC, as randomised)	129/273 (47.3%)	69/273 (25.3%)	20.9%	13.3%	28.5%

[a] Treatment difference and confidence interval weighted for the size of PI strata and ENF strata

[b] Significant difference between treatment groups at p<0.0001; LL (lower limit) UL (upper limit)

n= number of responders, N=number of evaluable patients

The superiority of TPV/r ($p<0.001$) over the comparator is consistently demonstrated in the sensitivity analysis performed (excluding the On-treatment analysis however the results should be interpreted with particular caution due to a very limited number of patients in the comparator arm).

This superiority could even be concluded over each of the boosted PI (to the exception of the indinavir arm whose sample is far too limited to be satisfactorily analysed).

Table 11: Resist 2: Analysis of virologic response at week 16 (VR16) and treatment response at week 24 (TR24) and sensitivity analysis of VR16 and TR24-(as randomised)

	Treatment group						Treatment difference[a]		
	TPV/r			CPI/r			95% CI		
	n	(%)	N	n	(%)	N	Weighted Diff.(%)	LL(%)	UL(%)
Key analyses									
- *VR16 – FAS (NCF, as randomised)*	204	(46.9)	435	91	(21.3)	428	(25.0)[b]	(18.9)	(31.1)
- TR24 – FASS24 (NCF as randomised)	111	(41.0)	271	40	(14.9)	268	(25.0)[b]	(17.8)	(32.2)
Sensitivity analyses for virologic response at week 16									
VR16 – PPS16 (NCF, as randomised)	138	(48.6)	284	62	(23.4)	265	(24.5)[b]	(16.8)	(32.2)
- *FAS (TPV-NCF CPI-NCC, as randomised)*	204	(46.9)	435	89	(22.5)	395	(23.7)	(17.5)	(30.0)
- FAS (NCC, as randomised)	204	(50.5)	404	89	(22.5)	395	(27.4)	(21.0)	(33.8)
- FAS (OT, as randomised)	199	(51.0)	390	87	(27.4)	318	(22.8)	(15.8)	(29.8)
Sensitivity analyses for treatment response at week 24									
TR24 – PPSS24 (NCF, as randomised)	80	(44.4)	180	31	(18.6)	167	(24.6)[b]	(15.4)	(33.8)
- FASS24 (TPV-NCF CPI-NCC, as randomised	111	(41.0)	271	40	(15.3)	261	(24.6)	(17.4)	(31.9)
- FASS24 (NCC, as randomised	111	(42.4)	262	40	(15.3)	261	(26.1)	(18.7)	(33.4)
- Confirmed virologic response – FASS24 (OT, as randomised)	109	(49.8)	219	41	(32.0)	128	(17.1)	(6.7)	(27.5)
- Confirmed virologic response – FASS24 (OT, as randomised)	113	(47.5)	238	42	(17.4)	241	(29.3)	(21.4)	(37.2)

a Treatment difference and confidence interval weighted for the size of enfuvirtide and PI strata
b Significant difference between treatment arms at $p<0.001$
n= Number of responders
N= Number of evaluable patients
Treatment difference and confidence interval weighted for the size of enfuvirtide and PI strata
VR16 Unconfirmed virologic response at Week 16

The efficacy results demonstrated the superiority of the TPV with RTV treatment group whatever the population analysis. Even in the FASS24 on-treatment analysis, the difference was statistically significant in favour of the TPV with arm despite the imbalance on study discontinuations due to virologic failure between both arms. However, this analysis should be interpreted with caution since the FASS24 population does not include the total study population (approximately 60% of the study population). The results on the whole population are presented in table 12.

In this study, a slightly higher number of patients in the TPV/r arm received concomitant enfuvirtide compared with patients in the CPI/r arm. This addition could have a small impact favouring TPV/r, however, the different sensitivity analyses support that TPV/r achieved better results across all efficacy endpoints than CPI/r, regardless of enfuvirtide use.

At the time of the submission of the responses to the list of questions, the applicant submitted to the CHMP preliminary results at 48 weeks for RESIST 1 and additional 24 weeks for RESIST 2 (Tables 12 and 13).

Table 12: RESIST 1: primary endpoint efficacy results at weeks 48

	Treatment group						Treatment difference			
	TPV/r			CPI/r			95 % CI			
	n	(%)	N	n	(%)	N	Weighted diff (%)	LL (%)	UL (%)	p-value
Key analysis										
FAS (week 24, NCF, as randomised	130	41.8	311	74	23.9	309	17.0	10.0	24.1	<.0001
FAS (week 48, NCF, as randomised	103	33.1	311	49	15.9	309	16.8	10.3	23.2	<.0001
Sensitivity analysis										
PPS (week 48) (NCF, as randomised)	66	35.7	185	38	19.7	193	15.6	6.9	24.2	0.0004

n = number of responders; N= number of evaluable patients; Treatment difference and confidence interval weighted for the size of enfuvirtide and PI strata.

Table 13: RESIST 2 primary endpoint efficacy results at weeks 24

	Treatment group						Treatment difference			
	TPV/r			CPI/r			95 % CI			
	n	(%)	N	n	(%)	N	Weighted diff (%)	LL (%)	UL (%)	p-value
Key analysis										
FAS (week 24, NCF, as randomised	177	40.7	435	76	17.8	428	22.3	16.4	28.1	<.0001

n = number of responders; N= number of evaluable patients; Treatment difference and confidence interval weighted for the size of enfuvirtide and PI strata.

The per protocol analyses at 24 weeks for all different subgroup analyses, combining data from both studies confirmed the results seen with the full set analysis.

The analysis of treatment response by enfuvirtide stratum show a higher response rate in the tipranavir arm, with a bigger difference between both arms in the stratum of patients treated with enfuvirtide (Table 14).

Table 14: Treatment response at Week 24 by ENF stratum – RESIST trials (PPSS24)

	Treatment Group					
	TPV/r			CPI/r		
	n	(%)	N	n	(%)	N
Enfuvirtide Use						
. No	111	(39.1)	284	61	(21.1)	289
. Yes	55	(63.2)	87	20	(28.2)	71

n = Number of responders; N = Number of evaluable patients

Among the relevant protocol deviations, the so called “wrong T20 stratum” (prescribers changed their mind before and after randomization on the need to add enfuvirtide) was the most concerning. Given the very limited number of these deviations (21 in the TPV/rtv arm and 28 in the comparator arm), they were unlikely to have significantly impacted the efficacy demonstration.
A particular concern emerged that prescribers might have chosen to select a suboptimal management of the patients in the comparator arm so that patients could benefit earlier switch to the TPV with ritonavir arm in the roll-over study 1182.17. This attitude could have biased the demonstration of the superiority of TPV with RTV over the comparator arm. To solve this concern the applicant provided the individual data of all patients who have switched from the RESIST trials to the rollover study 1182.17 together with the analysis of the potential biases. The computerized checking of the data provided re-assurance that sub-optimal therapeutic management in the comparator arm was marginal and therefore unlikely to have altered demonstration of superiority of TPV with RTV over the comparator arm.

Table 15 presents treatment response for the overall population and detailed by PI strata for the subgroup of patients with genotypically resistant strain.

Table 15: treatment response* at week 24 (pooled RESIST-1 and RESIST-2)

RESIST study	**APTIVUS/RTV**		**CPI/RTV****		**p-value**
	n (%)	**N**	**n (%)**	**N**	
Overall population					
FAS	240 (41.2)	582	109 (18.9)	577	<0.0001
PP	166 (44.7)	371	81 (22.5)	360	<0.0001
- with ENF (FAS)	92 (58.2)	158	33 (25.8)	128	<0.0001
- without ENF (FAS)	148 (34.9)	424	76 (16.9)	449	<0.0001
Genotypically Resistant					
LPV/rtv					
FAS	69 (36.9)	187	29 (14.6)	199	<0.0001
PP	46 (39.0)	118	20 (16.3)	123	<0.0001
APV/rtv					
FAS	48 (42.9)	112	21 (17.9)	117	<0.0001
PP	37 (45.7)	81	14 (18.7)	75	0.0003
SQV/rtv					
FAS	30 (52.6)	57	9 (17.0)	53	<0.0001
PP	18 (51.4)	35	3 (12.0)	25	0.0002
IDV/rtv					
FAS	8 (61.5)	13	1 (6.3)	16	0.0005
PP	4 (66.7)	6	1 (7.7)	13	0.0046

* Composite endpoint defined as patients with a confirmed 1 log RNA drop from baseline and without evidence of treatment failure

A summary of the secondary endpoints is presented in table 16.

Table 16: Summary of secondary efficacy endpoints: RESIST –1 and RESIST-2 studies

	RESIST-1		RESIST-2*		Total	
	TPV/r	CPI/r	TPV/r	CPI/r	TPV/r	CPI/r
Total treated	N= 311	N=309	N=271	N=268	N=582	N=577
VL >= 1 log_{10} Reduction (NCF)	43.4%	23.3%	43.9%	17.2%	43.6%	20.5%
VL <400 copies/ml (NCF)	34.7%	16.5%	33.6%	13.1%	34.2%	14.9%
VL <50 copies/ml (NCF)	25.1%	10.0%	22.5%	8.6%	23.9%	9.4%
Median Baseline VL change (LOCF) [log_{10} copies/ml]	-0.88	-0.28	-0.72	-0.22	-0.80	-0.25
Median change CD4+ cell count [cells/mm3] (LOCF)	36	6	31	1	34	4

* preliminary data at 24 weeks

The analysis of the resistance data was presented under the pharmacodynamic section of the clinical efficacy part of this document.

Hepatitis co-infected patients

In view of the very limited number of patients with hepatitis B or C virus co-infection it is not possible to draw any firm conclusion. Even if the efficacy data do not raise any signal towards a lower response rate, the pronounced hepatotoxicity of the product should be kept in mind and will require particular caution in clinical practice as reflected in the SPC.

Long term data

The preliminary 48 weeks descriptive data are encouraging as regards the durability of the virological response in the TPV with RTV arm. However, the formal 48 week analysis of the combined RESIST studies is currently ongoing and will be submitted as specific obligation to be fulfilled post-authorisation.

Paediatric patients

The data are currently insufficient to demonstrate efficacy in children however the applicant undertook to provide additional data in this population as part of the follow-up measures to be fulfilled post-authorisation.

Supportive study

The study 1182.51was an open-label, 1:1:1 randomised, parallel-group pharmacokinetics trial of TPV with RTV, alone or in combination with RTV-boosted saquinavir (SQV), amprenavir (APV), or lopinavir, plus an optimised background regimen, in multiple antiretroviral experienced patients. It mainly aimed at exploring the influence of the co-administration with boosted PIs on the PK parameters of tipranavir/ritonavir and reciprocally.

Overall, the patients were well-balanced between the treatment groups in terms of gender, race and age. Most patients were male (93.3%) aged between 41 and 55 years of age. As for RESIST studies, the target population is at an advanced stage of the disease (60% at CDC stage C).
The median number of ARVs taken by the study patients was overall equal to 13 (range 7-19): 5NRTIs (range 0-3), 2NNRTs (range 0-3) and 5 Pis (range 2-7).
The tipranavir arm was compared to other boosted PI at week 2. After week 2 tipranavir/ritonavir was added to each of the boosted PI arm.
In the week 2 assessment (i.e. before the addition of the boosted PI to the TPV/r) results favoured the TPV/r arm in comparison to other boosted PIs (including LPV/r). This likely reflects that in heavily pretreated patients with resistant strain, TPV/r characterised by a limited cross resistance will have a better potential to achieve virological suppression. After week 2, the benefit of a dual ritonavir-boosted protease inhibitor is not clearly apparent with regard to the virologic response results. However, this has to be analysed in the light of the PK parameters that show a significant interaction between tipranavir/ritonavir and the boosted PI (decrease in exposure).

Clinical safety

- Patient exposure

More than 4,000 patients have been included in the clinical programme.

The number of HIV-positive patients and HIV-negative subjects exposed to at least 1 dose of TPV from the 39 trials at the time of the individual trial cut-off dates was 3195 (2430 HIV-positive patients and 765 HIV-negative subjects).

In pharmacological studies, 765 healthy subjects have been exposed to TPV. In clinical studies, 2430 HIV infected patients received TPV containing treatment regimen, 761 patients at the recommended dose of 500mg/200mg TPV/r bid for more than 24 weeks, 57 for $\geq$ 48 weeks and 6 for $\geq$ 96 weeks. More than 60% of the total person exposure years in HIV-positive patients (n =1854) occurred with the intended market dose of TPV/r 500 mg/200 mg (685.1 of 1101.5 exposure years to TPV). Of the 685.1 patient years of exposure, over 40%, (300.3 years) are from the RESIST trials. Treatment exposure from the RESIST trials was approximately 13% higher in the TPV/r group (300.3 years) compared with the CPI/r group (264.6 years) up to 24 weeks.
Overall, for HIV-positive patients, the median age of TPV/r patients was 43.0 years (98.5% were between the ages of 18 to 64 years; the majority of the patients (87.4%) were males, White Caucasians (80.6%); with a mean baseline HIV RNA level of 4.79 $\log_{10}$ copies/ml, and a mean CD4+ cell count of 187 cells/mm^3.

In the update period, 793 HIV-positive patients have been added to the program, predominantly in a recently initiated treatment naïve patient trial and the emergency use/expanded access programs.

In the update period, median duration of exposure to TPV/r increased from 168 days (n = 1854) to 322 days (n = 1870), and total patient exposure years increased 1.6 fold, from 1102 to 1759 years. Of

these, 1,397 HIV-positive patients were treated with TPV/r 500 mg/200 mg BID for a total of 685 patient exposure years (PEY); and 55% of these patients were treated for more than 24 weeks, with a maximum exposure of more than 5 years.

From the RESIST trials, all available safety data up to the 30 September 2004 cut-off were included and median duration of exposure for TPV/r patients increased 2 fold, from 168 days (n = 746) to 330 days (n = 748), while that for CPI/r patients increased 1.4 fold, from 124 days (n = 737) to 172 days (n = 737). Total patient exposure years increased 2 fold in the TPV/r group, from 300 to 615, and 1.5 fold in the CPI/r group, from 265 to 406. The number of discontinuations from the CPI/r arm of RESIST continues to be higher than that of the TPV/r arm.
In the RESIST trials, patients in the CPI/r arms with documented evidence of virologic failure were allowed to discontinue treatment after Week 8 and to receive TPV/r in the long-term safety rollover study, 1182.17. As reported in the SCS, the number of patients continuing treatment was 639 (85.7%) of 746 patients in the TPV/r arm and 357 (48.4%) of 737 patients in the CPI/r arms. As of 30 September 2004, 524 (70.1%) of 748 patients in the TPV/r arm and 231 (31.3%) of 737 patients in the CPI/r arms were continuing in the RESIST trials. During the update period, premature discontinuations increased 2 fold in the TPV/r group, from 14.3% to 29.9% and 1.3 fold in the CPI/r group, from 51.6% to 68.7%. The most common reason for discontinuation of study medication in the CPI/r group was due to lack of efficacy (316/737 patients; 42.9%), compared with the TPV/r group (68/748 patients; 9.1%).

- Adverse events

In pharmacological studies, among healthy subjects exposed to TPV, 674 (88.1%) experienced AEs.

In clinical studies, among patients who received the recommended dose of 500mg/200mg TPV/r bid for more than 24 weeks, 615 (80.8%) experienced at least one AE. The duration of exposure in clinical trials was between 24 and 96 weeks.

In the update period, the types and rates of adverse events (AEs) and serious AEs reported among TPV/r-treated patients in the integrated trials and in the comparative RESIST trials, essentially did not change despite increased patient exposure, and were consistent with those of other currently available protease inhibitors.
In the RESIST trials, the most common AEs across both treatment arms were gastrointestinal disorders, which increased from 47.1% to 56.6% in TPV/r patients and from 42.9% to 48.2% in CPI/r patients during update period, followed by infections and infestations, which increased from 43.8% to 53.9% in TPV/r patients and from 37.2% to 44.1% in CPI/r patients during the update period. For drug related events of any severity, the most frequently reported AEs for both treatment groups were diarrhoea, which increased from 13.4% to 14.6% in TPV/r patients and from 11.1% to 11.4% in CPI/r patients during the update period, and nausea, which increased from 11.7% to 12.4% in TPV/r patients and from 7.9% to 8.4% in CPI/r patients during the update period, however these AE rates have not been adjusted for duration of exposure.
Headache was reported by 11.1% of 1854 patients who received TPV/r for 1101.5 PEY. When considering causality, headache was considered related to TPV/r in 4.1% of the 1854 patients. Within the RESIST trials that allow comparison of TPV/r to standard PI therapy, headache is reported in 10.5% of 746 TPV/r patients (300.3 PEY) and in 7.3% of 737 CPI/r patients (264.6 PEY) at the 24-week analysis. While headache is commonly reported in TPV/r recipients, it is seldom serious and usually does not lead to discontinuation of therapy.

Although individual variability in the type and frequency of AEs was observed in evaluation of AEs by gender and race, clinically, no unusual AE patterns or other safety concerns were identified in the RESIST trials that would suggest that TPV/r should be restricted or have the dose adjusted based on these factors.

A signal was raised from non clinical data that TPV could induce coagulation disorders. TPV was observed to increase coagulation parameters (i.e. prothrombin, time and activated partial thromboplastin time) in rodents and provoked excessive haemorrhage. This was especially critical, since TPV is synthetised on the structural basis of coumarin-like anticoagulants agents (warfarin and

phenprocoumon). In the 24-week an exploratory analysis of collective terms associated with "bleeding", there were 29 (3.9%) bleeding events in the TPV/r arm and 13 (1.8%) in the CPI/r arm. The relative risk of bleeding was significant at 24-week analysis (1.98; 95% CI = 1.03-3.80) and was still perceivable as a trend even in the 48 weeks analysis. This safety issue will be further explored in the post-authorisation phase.

- Laboratory findings

Most safety laboratory values are not affected by treatment with TPV/r. Grade 3 or 4 elevations in ALT/AST were more common with TPV/r than CPI/r. At 24 weeks, as reported in the SCS, 6.2% of TPV/r patients as compared to 2.5% of CPI/r patients had Grade 3 or 4 ALT and/or AST elevations. In the update period, the frequency increased by ~50% in the TPV/r group (9.8% Grade 3 or 4 ALT and/or AST) and increased only by 20% in the CPI/r group (3.0%). Grade 3 or 4 LFT abnormalities were generally asymptomatic and most patients continued treatment without permanent discontinuation. Relevant risk factors associated with the development of Grade 3 or 4 ALT/AST abnormalities included treatment with TPV/r, positive results at baseline for hepatitis Bs Ag and/or hepatitis C RNA, baseline CD4+ cell counts >200 cells/mm^3, and baseline Grade 2 or higher liver test abnormalities.

Grade 3 or 4 elevations in cholesterol and triglycerides were more common with TPV/r. At 24 weeks, as reported in the SCS, 3.3% TPV/r patients as compared to 0.3% CPI/r patients had cholesterol levels >400 mg/dl, and 20.8% TPV/r patients as compared to 11.2% CPI/r patients had triglyceride levels >750 mg/dl. In the update, the frequency of Grade 3 or 4 cholesterol elevations has increased to 4.0% in TPV/r patients as compared to 0.4% in CPI/r patients, and Grade 3 or 4 triglyceride elevations have increased to 23.3% in TPV/r patients as compared to 12.2% in CPI/r patients. This will have to be followed in the Periodic Safety Update Reports and the 48 and 96 weeks reports on the RESIST trials.

- Serious adverse event/deaths/other significant events

The frequency of cumulative SAEs in the 2MSU as compared to the SCS increased in the TPV/r group from 13.1% to 18.9%, and increased in the CPI/r group from 11.9% to 14.7%. SAEs associated with liver events, were observed in 14 (1.9%) TPV/r patients as compared to 2 (0.3%) CPI/r patients.
In the SCS, 102 fatalities were reported for the entire development program up through the 11 June 2004 cut-off. In the update period of 12 June 2004 to 30 September 2004, 29 additional fatalities were reported, for a total of 131 fatalities in the program. Of the 131 fatalities, 104 were in patients treated with TPV/r, thus, the overall frequency of death among TPV/r treated patients is 3.1% (104 deaths in 3,367 TPV/r treated patients). The types and rate of fatalities in the TPV/r development program are consistent with what is expected in patients with advanced HIV disease. Fatalities were predominantly associated with AIDS progression events or opportunistic infections. However, among the fatalities in TPV/r treated patients several included a hepatic component in which the role of TPV/r could not be ruled out.
The frequency of deaths in the RESIST trials was higher for TPV/r patients (3.3%) than CPI/r patients (1.9%). After being adjusted for exposure, the estimated number of patient deaths per 100 PEY was 4.1 for patients receiving TPV/r and 3.5 for patients receiving CPI/r.

Hepatic events

There is a high incidence (47%) of hepatotoxicity/hepatic disorders (mainly cytolytic):
(865/1861 (47%) patients had higher ALT grade in comparison with baseline ALT grade, while 996 did not have a change in ALT grade in comparison with baseline,
More ALT grade shifts were observed in patient with higher baseline ALT grade (2.8% from grade 0 to grade 4; 4.2% from grade 1 to grade 4, and finally 8.5% from grade 2 to grade 4). The median time to maximum in days is longer when baseline ALT grade is low. 50% of 26 patients who temporarily interrupted TPV/r had a positive re-challenge, increased to grade 3 or greater, after a median of about 30 days. 83/87 patients with grade 3 or greater and who stopped tipranavir/r had a decrease to <grade 3 with a median time to achieve an ALT grade 2 or lower of 22 days.

Except for viral hepatitis B and/or C, no specific risk factors have been found although the baseline ALT grade appears to be a risk factor. The mechanism of hepatotoxicity remains unknown.
As seen in the dose response study, there was a trend toward a dose relationship of hepatic enzyme elevations.
The hepatoxicity is a major concern with TPV. Therefore the CHMP agreed on introducing strong warnings and stringent monitoring of hepatic tests prior and during treatment as specified in the Summary of Product Characteristics, on the need for quarterly reviews of hepatic disorders as well as for further data to better define the monitoring.

Lipodystrophy

In the combined RESIST trials, a "fat redistribution" AE was self-reported in 1.9% and 0.4% of patients in the TPV/r and CPI/r groups, respectively, during the course of the studies. Compared to CPI/r treatment, the overall relative risk of "fat redistribution" for TPV/r treatment was 4.14 (95% CI = 1.19, 14.4). The greatest relative risk for "fat redistribution" was seen in the time interval of >12 to 24 weeks, in which the relative risk was 6.15 (95% CI = 0.77, 49.2). No standardised criteria for lipodystrophy were adopted in the RESIST pivotal studies. As already mentioned lipid metabolism disorders will be further explored during the post-authorisation phase.

Rash

High frequency of rash was observed in an interaction study (BI 1182.22) performed in healthy, female volunteers. In that study 32/42 women taking both tipranavir/ritonavir with oral contraceptives reported a rash requiring early discontinuation form the study before receiving the final dose. No Stevens Johnson or Lyell Syndrome was reported. In the dose finding study 1182-52 in HIV infected patients it was assumed that high TPV concentrations was a risk factor for developing rash (OD 1.02; 95 % CI 1.00 to 1.03; p = 0.01). A warning has been included in the SPC, and the applicant undertook to further explore this safety issue in post-authorisation phase.

Pregnancy

There have been seven known cases of TPV/r exposure during pregnancy, the outcomes for these included 4 live normal births, 2 elective terminations, and 1 spontaneous abortion. The applicant undertook to support the Anti-Retroviral Pregnancy Registry intended to detect early any potential risks of teratogenicity associated with antiretroviral therapy.

Cardiotoxicity
The available electrocardiographic data do not suggest an increased risk of QTc prolongation for patients taking tipranavir. Nonetheless, considering the limitations of the clinical exploration of the cardiotoxic potential, the applicant undertook to conduct a formal study to evaluate of the QT interval after administration of TPV with RTV, the results of which will be provided post-authorisation.

Long term cardiovascular risk

No particular signal has emerged toward a higher number of cardiovascular events. However, the follow-up is currently limited and cardiovascular events will have to be monitored in the long term.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled

in a satisfactory way, and these results lead to the conclusion that the quality of this product is considered to be acceptable.
At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, but which will have to be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Non-clinical pharmacology and toxicology

Tipranavir has 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. Tipranavir demonstrated antiviral activity against several resistant HIV-strains indicating that it may be a therapeutic opinion for PI-experienced HIV-patients. The general pharmacology studies showed no significant treatment related adverse effects.

The pharmacokinetics profile of tipranavir has been adequately studied preclinically. Results showed that RTV co-administration resulted in an increase in TPV systemic exposure in all tested species.

Studies with co-administration of tipranavir and ritonavir did not reveal any additional toxicological effects when compared to those seen in the tipranavir single agent toxicological studies. The predominant effects of repeated administration of tipranavir across all species toxicologically tested were on the gastrointestinal tract (emesis, soft stool, diarrhoea), and the liver (hypertrophy). Effects were reversible with termination of treatment. Additional changes included bleeding in rats at high doses (rodents specific). Bleeding observed in rats was associated with prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT). Further data are awaited in male rats to elucidate the mechanism of action of the anti-coagulant effect of TPV. The majority of the effects in repeat-dose toxicity studies appeared at systemic exposure levels which are equivalent to or even below the human exposure levels at the recommended clinical dose.
There was no evidence of toxicity to reproduction. Tipranavir showed no evidence of genetic toxicity in a battery of *in vitro* and *in vivo* tests. The lack of final results from the carcinogenicity studies was addressed and in accordance with the Note for Guidance on the need for Carcinogenicity Studies of Pharmaceuticals (CPMP/ICH/140/95), related to drugs intended for the treatment of patients with limited treatment options, the CHMP 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

Tipranavir is a new non-peptidic protease inhibitor. It has been developed in combination with
200 mg ritonavir as a pharmacokinetic enhancer to overcome its low bioavailability. Moreover, a particular SEDDS capsule formulation has been developed in this field. It has an attractive pharmacodynamic profile with limited cross resistance to other available protease inhibitors, that confers a particular value in the field of salvage therapy. Resistance data derived from ongoing studies will be provided to further substantiate the resistance profile of tipranavir during the post-authorisation phase.

Tipranavir is mainly characterised by a high variability and a complex interaction profile which requires particular attention in particular with other antiretroviral agents. Tipranavir is a PgP substrate, weak PgP inhibitor and potent inducer. In addition it is a substrate, inducer and inhibitor of CYP 3A4. Co-administered with low dose of ritonavir, there is a net inhibition of CYP3A4.
Awaiting for further data on the food influence on the pharmacokinetics of tipranavir, it was agreed to recommend the administration of tipranavir with food.
Since its renal clearance is negligible, no dose adjustment is recommended in patients with renal impairment. Because tipranavir is metabolised by the hepatic system, liver impairment may increase tipranavir exposure and thereby worsening its safety profile. Therefore patients with mild hepatic impairment should be closely monitored, with increased monitoring frequency of hepatic tests as reflected in the SPC. In the absence of adequate data tipranavir is contraindicated in patients with severe liver impairment as well as moderate waiting for results of a study in this population. The

applicant undertook to conduct additional studies to better define the pharmacokinetics profile of tipranavir in particular with respect to interactions.

With respect to the choice of the dose, whereas higher doses seemed to be associated with better virological suppression, hepatic events are a concerning limiting factor for increasing the dose. The choice of 500/200 mg was therefore considered appropriate.

The clinical benefit of tipranavir has been evaluated in two large, multicentre, open label phase III studies (around 600 and 800 patients enrolled each in RESIST 1 and 2) that included patients previously treated with multiple antiretroviral regimens. Patients enrolled were randomised to receive a 500 mg/200 mg twice daily dose of tipranavir combined with ritonavir or another protease inhibitor combined with ritonavir at its standard boosting dose. In addition, patients received an optimised background regimen selected on the basis of treatment history and baseline genotypic resistance testing. The population enrolled was to match precise inclusion criteria as regards the genotypic resistance at baseline. In practical, an heterogeneous population of heavily pre-treated patients has been enrolled (with or without any remaining "genotypically available" boosted PI). The use of enfuvirtide was allowed, if chosen prior to randomisation. Although not designed in this way, it turned out that for both studies "best available boosted PI" that could be proposed to the patient was lopinavir/ritonavir.
In both studies tipranavir/ritonavir has been shown to be superior ($p<0.001$) to a mixed comparator of PI boosted. At 24 weeks, more patient on tipranavir had a -1 $\log_{10}$ copies/ml decrease in plasma viral load (41.5 versus 22.3 % ; $P< 0.0001$ in RESIST 1). At 16 weeks, more patient on tipranavir had a -1 $\log_{10}$ copies/ml decrease in plasma viral load (46.9 versus 21.3 % ; $P< 0.0001$ in RESIST 2). Preliminary data at 48 weeks for RESIST 1 and 24 weeks for RESIST 2 suggest the maintenance of the superiority of tipranavir. Despite the complex design of the studies, re-assurance was provided, notably with the checking of individual data, showing that the superiority has not been biased in favour of tipranavir arm.

Limited data are available on the use of tipranavir in patients co-infected with hepatitis B or C. Because this population is at increased risk for severe and potentially fatal hepatic adverse events, tipranavir should be used in this population only if necessary with an increased clinical and laboratory monitoring awaiting for further data.

There are currently insufficient data to support the use of tipranavir in children but the applicant undertook to complete the development programme in this population.

Safety

In the RESIST trials, the most frequent adverse reactions were diarrhoea, nausea, fatigue, headache and vomiting in the tipranavir arm. The safety profile of the tipranavir is mainly characterised by its hepatotoxicity, lipid disorders, rash and coagulation disorders/bleeding. These reactions have been seen at higher frequency among the tipranavir arm compared to the comparator arm in the RESIST trials. The applicant provided its plan to further follow these issues during the post-authorisation phase. In addition with respect to the liver toxicity, as already mentioned, strong warnings and stringent monitoring of hepatic tests prior and during treatment have been specified in the Summary of Product Characteristics, and quarterly reviews of hepatic disorders and deaths as well as for further data to better define the monitoring will be provided during the post-authorisation phase.

Benefit/risk assessment

Overall, these pivotal studies have demonstrated that tipranavir/ritonavir is a valuable therapeutic option in salvage regimen in line with its pharmacodynamic properties. The development of this product is in line with the Guideline on the clinical development of anti-HIV medicinal products for heavily treatment-experienced patients with few remaining treatment options for which there is an unmet medical need. In line with the Guideline, awaiting for the 48 weeks data from the RESIST trials to confirm the efficacy and safety of long term use of tipranavir with low dose of ritonavir, the marketing authorisation could be recommended under exceptional circumstances. Nonetheless in view

of its safety profile and complex interaction profile, the CHMP recommended that tipranavir with low dose of ritonavir should be considered as a last line PI therapy and should be used only when documented resistance precludes the administration of other protease inhibitors.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit/risk ratio of APTIVUS was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances in the following indication

> "APTIVUS, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.
>
> This indication is based on the results of two phase III studies, performed in highly pre-treated patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors (see details of resistance profile of patients' HIV at baseline in section 5.1 *of the Summary of Product Characteristics*).
>
> In deciding to initiate treatment with APTIVUS, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of APTIVUS."